Task History

June 22, 2011 10:39 PM

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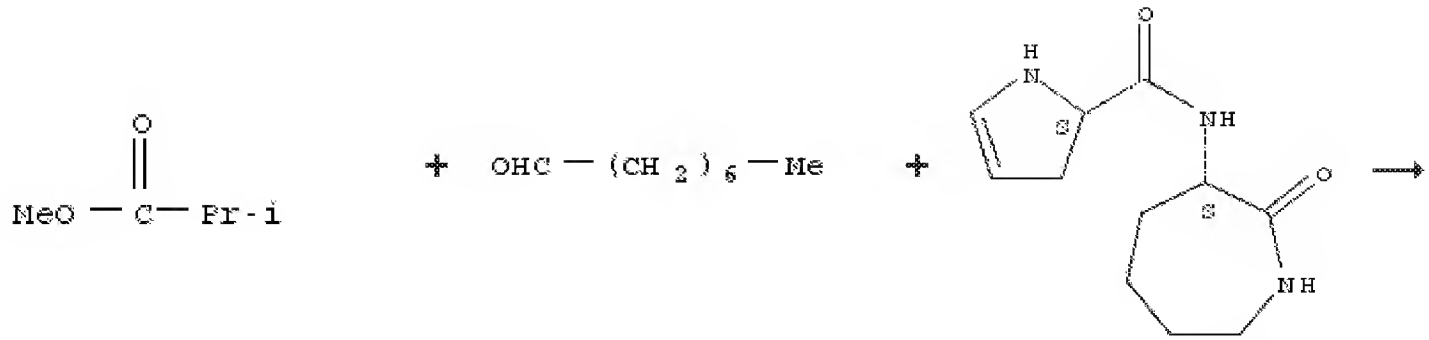
Answer set 9 created with 1 reference answer from CAPLUS

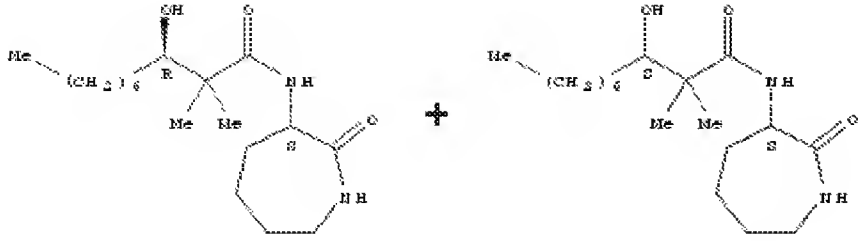
Retrieve reaction information in 1 reference of Answer set 9

Answer set 10 created with 76 reactions

1. 3 Steps



{Step 3.2}



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 45 min, -78°C

1.2 18 h, -78°C → rt

1.3 R:NH_4Cl, S:H_2O, rt

2.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

2.2 S:H_2O, pH 2

3.1 R:1-Benzotriazolol, R:EtN=C=N$(CH_2)_3NMe_2$•HCl, S:THF, 4 h, rt

3.2 R:Disodiumcarbonate, S:H_2O, 18 h, rt

Notes

1) reaction from p.46 in patent, 2) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.46 in patent, 3) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 3, Reagents: 6, Solvents: 3, Steps: 3, Stages: 7, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

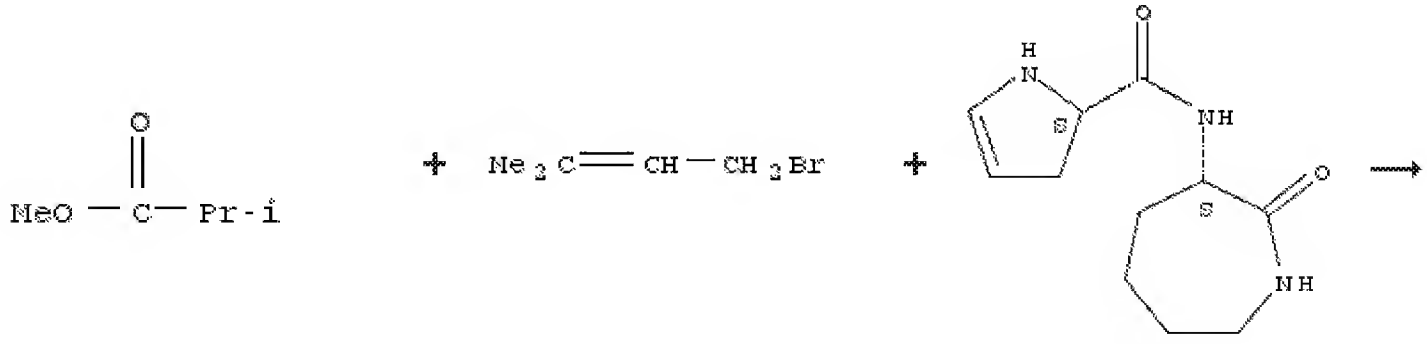
Step 1

Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at-78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacua and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4. The organic layer was dried over Na2SO4 and the solvent was removed to give methyl 2,2- dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δH (400 MHz, CDCl3) 3.70 (3H, s, OCH3), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH2)8), 1.19 (3H, s, CCH3), 1.17 (3H, s, CCH3) and 0.88 (3H, t, J 7 , CH2CH3) (no OH observed).

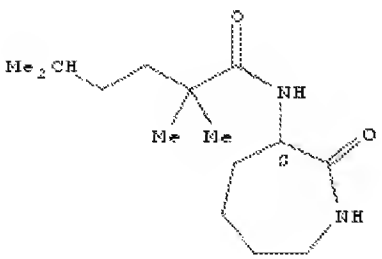
Step 2
Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and extracted with diethyl ether. The solution was dried over Na2SO4 and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 C; δH (400 MHz, CDCl3) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH2)8 + C(CH3)2) and 0.88 (3H, t, J7, CH2CH3).

Step 3
Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na2CO3 (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and dilute aqueous sodium hydroxide, and then dried over Na2SO4 and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'- hydroxy-2',2'-dimethyldecanoyl)amino-caprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δH (500 MHz, CDCl3) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH2, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH2, both isomera), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH ×2, both isomers), 1.60- 1.17 (21H, m, lactam CH ×2 + chain (CH2)8 + CH3, both isomers), 1.14 (3H, s, CCH3, both isomers) and 0.84 (3H, t, J 7, CH2CHs, both isomers); δc (125 MHz, CDCl3) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH3)2), 42.1, 42.0 (NCH2), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (×4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH2), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH3).

2. 4 Steps



[Step 3.1]



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

2.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

3.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

4.1 R:H_2, C:Pd(OH)$_2$, S:AcOEt, 14 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, 3) reaction from p.30 in patent, 4) reaction from p.30 in patent, Reactants: 3, Reagents: 5, Catalysts: 2, Solvents: 5, Steps: 4, Stages: 6, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1

Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N2. The reaction was stirred at - 78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) and hexane (3 x 250 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). νmax/cm-11732 (CO); δH (400 MHz, CDCl3) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH3), 2.20 (2H, d, J7.5, CHCH2, 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH3)2CO); δC (125 MHz, CDCl3) 178.4 (CO), 134.1 (Me2OCH), 119.8 (Me2C=CH), 51.6 (OCH3), 42.8 (Me2CCO), 38.7 (CH2), 25.9, 24.7 (x 2), 17.8 (CCH3); m/z (MH+ C10H19O2 requires 171.1385) 171.1388.

Step 2

2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

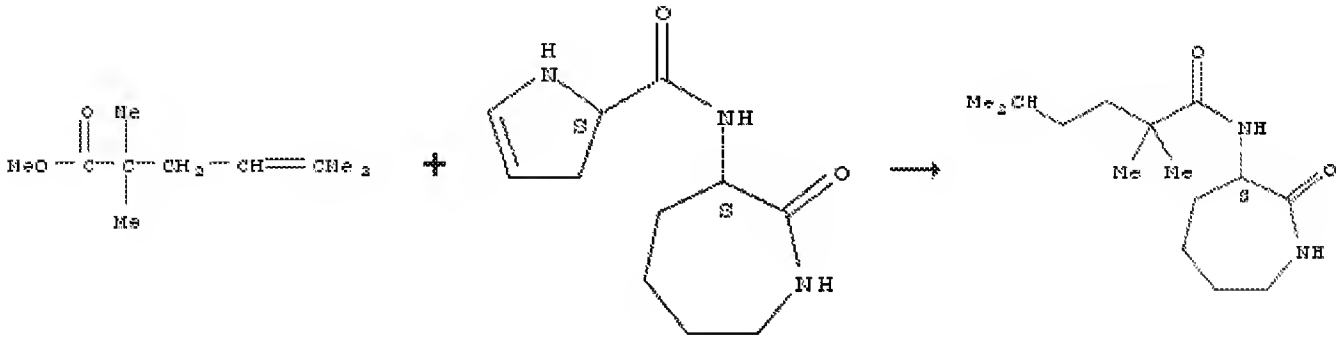
Step 3

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; νmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

Step 4

Example 24: (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmostsphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (6)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]25D (c=1, CHCl3) +27.8; νmax/cm-1 3249 (NH), 1654, 1638 (CO), 1502 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5.0, CHNH), 6.75-6.55 (1H, br m, CH2NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH2 + CH(CH3)2), 1.13 (3H, s, CH3), 1.12 (3H, 8, CH3), 1.08-1.02 (2H, m, CH2), 0.82 (3H, s, CH3), 0.80 (3H, s, CH3); δc (125 MHz, CDCl3) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH2N), 41.9 (CH2CMe2), 39.0, 33.7, 31.5, 28.9 (CH2), 28.4 (Me2CH), 27.9 (CH2), 25.3, 25.2, 22.6, 22.5 (CH3); m/z (MH+ C15H29N2O2 requires 269.2229) 269.2219.

3. 3 Steps



[Step 2.1]

Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

2.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

3.1 R:H_2, C:$Pd(OH)_2$, S:AcOEt, 14 h, rt

Notes

1) reaction from p.38 in patent, 2) reaction from p.30 in patent, 3) reaction from p.30 in patent, Reactants: 2, Reagents: 4, Catalysts: 2, Solvents: 4, Steps: 3, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

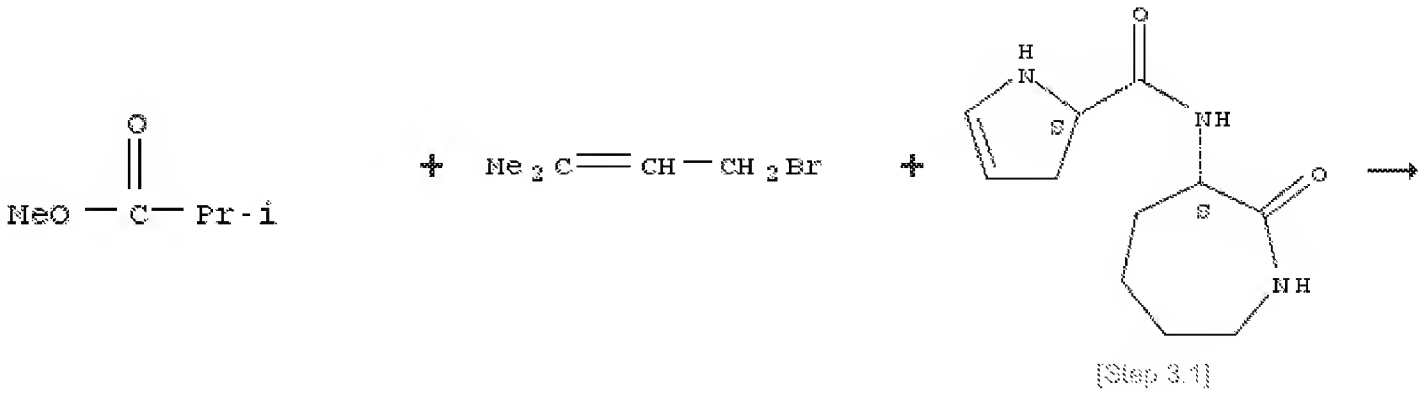
Experimental Procedure

Step 1
2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

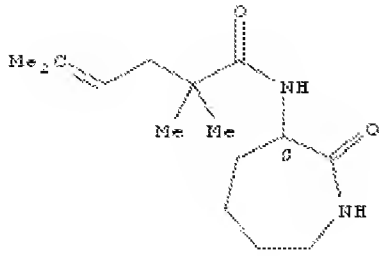
Step 2
Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; vmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

Step 3
Example 24: (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmostsphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (6)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]25D (c=1, CHCl3) +27.8; vmax/cm-1 3249 (NH), 1654, 1638 (CO), 1502 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5.0, CHNH), 6.75-6.55 (1H, br m, CH2NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH2 + CH(CH3)2), 1.13 (3H, s, CH3), 1.12 (3H, 8, CH3), 1.08-1.02 (2H, m, CH2), 0.82 (3H, s, CH3), 0.80 (3H, s, CH3); δc (125 MHz, CDCl3) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH2N), 41.9 (CH2CMe2), 39.0, 33.7, 31.5, 28.9 (CH2), 28.4 (Me2CH), 27.9 (CH2), 25.3, 25.2, 22.6, 22.5 (CH3); m/z (MH+ C15H29N2O2 requires 269.2229) 269.2219.

4. 3 Steps



[Step 3.1]



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

2.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

3.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, 3) reaction from p.30 in patent, Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 4, Steps: 3, Stages: 5, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1

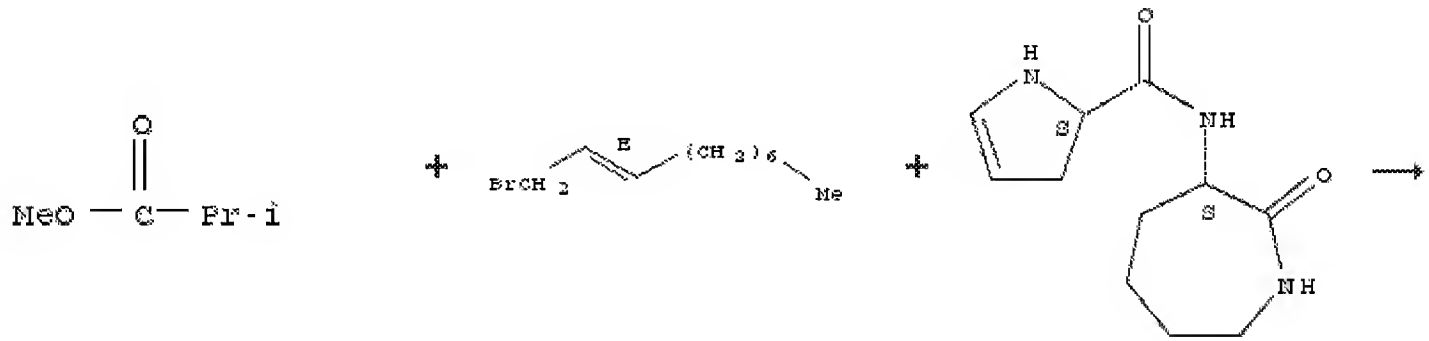
Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N2. The reaction was stirred at - 78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) and hexane (3 x 250 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). νmax/cm-11732 (CO); δH (400 MHz, CDCl3) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH3), 2.20 (2H, d, J7.5, CHCH2, 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH3)2CO); δC (125 MHz, CDCl3) 178.4 (CO), 134.1 (Me2OCH), 119.8 (Me2C=CH), 51.6 (OCH3), 42.8 (Me2CCO), 38.7 (CH2), 25.9, 24.7 (x 2), 17.8 (CCH3); m/z (MH+ C10H19O2 requires 171.1385) 171.1388.

Step 2

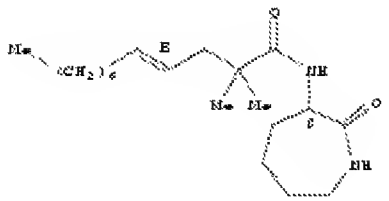
2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

Step 3
Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; vmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

5. 3 Steps



[Step 3.1]



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

2.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

3.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.36 in patent, 2) reaction from p.37 in patent, 3) reaction from p.29 in patent, Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 4, Steps: 3, Stages: 5, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Granger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

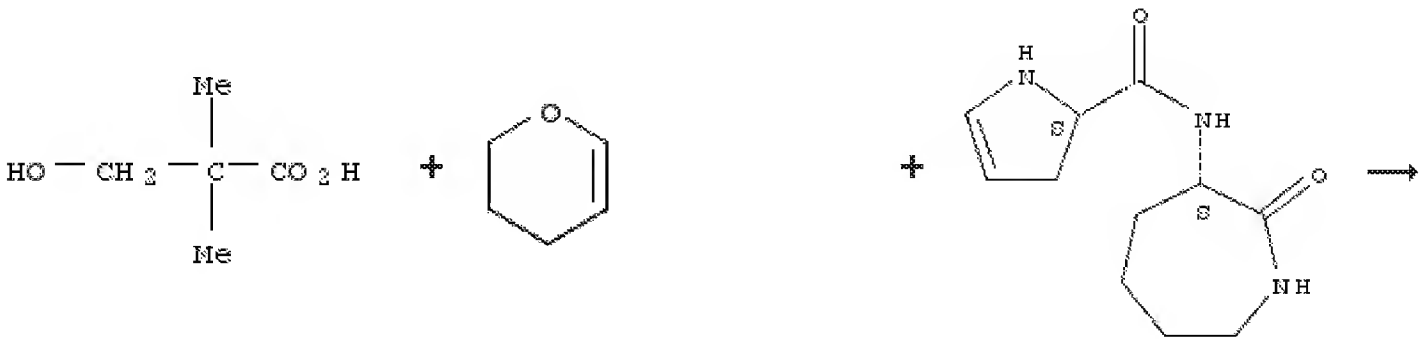
Experimental Procedure

Step 1
(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N2. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacua, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). νmax/cm-1 1734 (CO); δH (400 MHz, CDCl3) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dtt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH3), 2.18 (2H, dd, J7, 1, CH2CMe2), 1.96 (2H, br q, J6.5, CH2CH2CH=CH), 1.35-1.20 (10H, m, (CH2)sCH3), 1.14 (6H, s, C(CH3)2), 0.87 (3H, t, J 6.5, CH2CH3) δc (125 MHz, CDCl3) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH3), 43.6 (CH2), 42.6 (Me2CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH2), 24.7 (C(CH3) × 2), 22.6 (CH2), 14.1 (CH2CH3); m/z (MH+ C15H29N2O2 requires 241.2168) 241.2169.

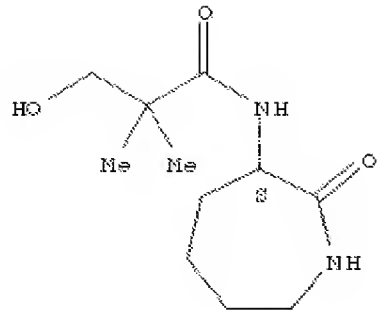
Step 2
(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the ether solvent removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (JE)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride**

Step 3
Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na2CO3 (3 0 mmol) in water (3 0 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). [α]25D (c = 1, CHCl3 +21.6; νmax/cm-1 3264 (NH), 1639 (CO), 1497 (NH); δH (500 MHz, CDCl3) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH2NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30- 3.17 (2H, m, CH2NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH2), 2.14 (1H, dd, 13.5, 7, CH=CHCH2), 2.01-1.87 (4H, br m, ring CH x2, + CH2CH=CH), 1.87-1.'74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH2)3) 1.1 3 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH2), 42.1 (x2)(CH2+ CMe2), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH2), 25.0, 24.8 (CH3) and 22.6 (CH3); m/z (MH+ C20H37N2O2 requires 337.2855) 337.2858.

6. 2 Steps



[Step 2.2]



Overview

Steps/Stages

1.1 R:p-$MeC_6H_4SO_3H$, S:CH_2Cl_2, 3 h, rt

1.2 R:KOH, S:H_2O, S:EtOH, 18 h, reflux

1.3 S:H_2O, pH 2

2.1 R:1-Benzotriazolol, R:Diimidazolylketone, S:THF, 4 h, reflux; reflux → rt

2.2 R:Disodiumcarbonate, S:H_2O, 18 h, rt

2.3 R:AcCl, S:MeOH, 18 h, rt

Notes

1) regioselective in stage 1, Na2SO4/NaHSO4 buffer used in stage 3, reaction from p.47 in patent, 2) reaction from p.48 in patent, Reactants: 3, Reagents: 6, Solvents: 5, Steps: 2, Stages: 6, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

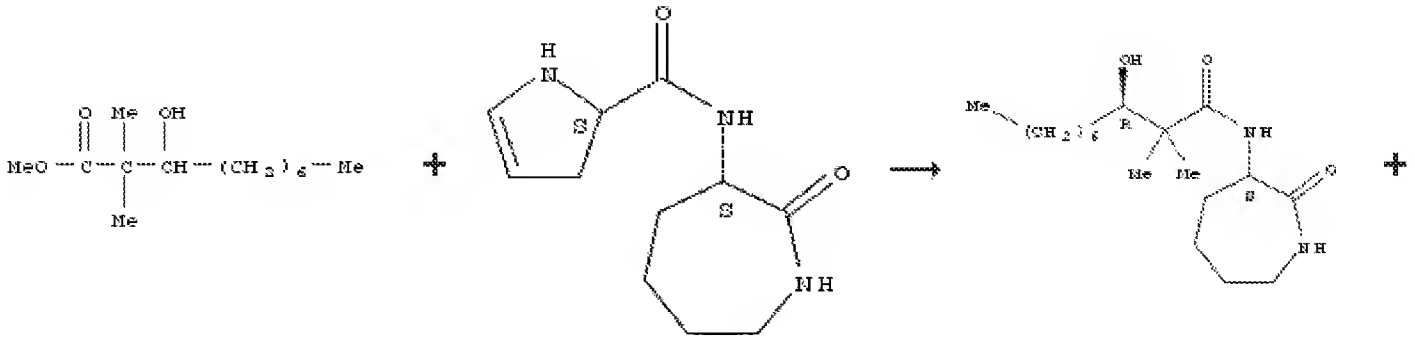
Step 1

Example 60: 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (Intermediate) 2,2-Dimethyl-3-hydroxy propionic acid (100 mmol) and 3,4-dihydro-2H-pyran (210 mmol) were dissolved in dichloromethane (50 ml), and para-toluenesulfonic acid (10 mg) was added and the reaction was stirred at ambient temperature for 3 hours. The reaction solvent was then removed and the residue was dissolved in ethanol (100 ml). A solution of KOH (120 mmol) in water (30 ml) was added and the reaction was heated at reflux for 18 hours. The reaction solvent was removed in vacua and the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4) and then extracted with diethyl ether. The diethyl ether layer was then dried over Na2SO4 and the solvent was removed in vacuo to give 2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid as an oil (20.0 g, >95%). 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propiomc acid, Yield (20.0 g, >95%). δH (400 MHz, CDCl3) 4.62 (1H, t, J 3.5, CHO2), 3.82 (1H, ddd, J 12, 9, 3, ring CH2O), 3.75 (1H, d, J 12, chain CH2O), 3.55-3.46 (1H, m, ring CH2O), 3.40 (1H, d, J 12, chain CH2O), 1.90-1.45 (6H, m, (CH2)3), 1.25 (3H, s, CH3) and 1.23 (3H, s, CH3).

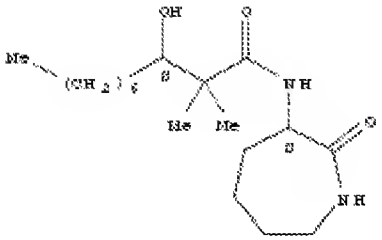
Step 2

Example 61: (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (4.65 mmol), 1-hydroxybenzotriazole monohydrate (4.65 mmol) and carbonyl diimidazole (4.50 mmol) were dissolved in THF (30 ml) and the reaction was heated at reflux for 4 hours. After the reaction was cooled to ambient temperature, a solution of(S,S)-3-amino- caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na2CO3 (15 mmol) in water (30 ml) was added and the reaction was stirred for 18 hours. The THF was then removed from the reaction by distillation in vacuo and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was dried over Na2SO4 and reduced in vacuo. The residue was dissolved in MeOH, and acetyl chloride (1 ml) was added. The reaction was stirred at ambient temperature for 18 hours, and then reduced in vacuo to give (S)- (2'-dimethyl-3'-hydroxy propionyl)amino-caprolactam as a solid (854 mg, 83%). (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam, Yield (854 mg, 83%). m.p. 97-99 °C; [α]25D (c = 0.5, CHCl3) +30.0; δH (400 MHz, CDCl3) 7.24 (1H, d, J 5.0, CHNH), 6.38 (1H, br s, CH2NH), 4.49 (1H, dd, J 10, 6, CHNH), 3.54 (1H, d, J 11, CHHOH), 3.49 (1H, d, J11, CHHOH), 3.33-3.20 (2H, m, CH2NH), 2.03-1.96 (2H, m, 2 × ring CH), 1.87-1.72 (2H, m, 2 × ring CH), 1.50-1.30 (2H, m, 2 × ring CH), 1.20 (3H, s, CH3) and 1.18 (3H, s, CH3); δc (125 MHz, CDCl3) 177.2, 176.0 (CO), 69.9 (CHOH), 52.1 (NHCHCO), 43.2 (CCO), 41.9 (CH2N), 31.1, 28.8, 27.9 (CH2 lactam), 22.4 and 22.3 (CH3).

7. 2 Steps



[Step 2 2]



Overview

Steps/Stages

1.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

1.2 S:H_2O, pH 2

2.1 R:1-Benzotriazolol, R:EtN=C=N$(CH_2)_3NMe_2$•HCl, S:THF, 4 h, rt

2.2 R:Disodiumcarbonate, S:H_2O, 18 h, rt

Notes

1) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.46 in patent, 2) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 2, Reagents: 4, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

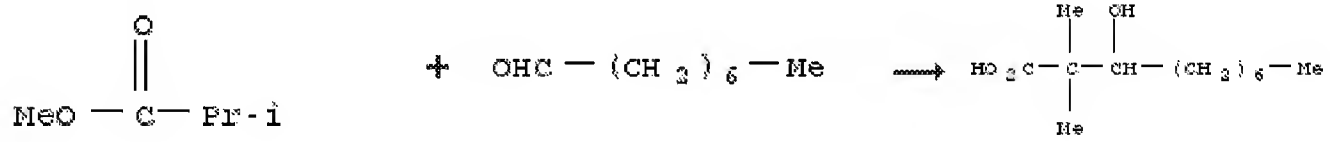
Experimental Procedure

Step 1

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and extracted with diethyl ether. The solution was dried over Na2SO4 and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 C; δH (400 MHz, CDCl3) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH2)8 + C(CH3)2) and 0.88 (3H, t, J7, CH2CH3).

Step 2
Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na2CO3 (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and dilute aqueous sodium hydroxide, and then dried over Na2SO4 and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'- hydroxy-2',2'-dimethyldecanoyl)amino-caprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δH (500 MHz, CDCl3) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH2, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH2, both isomera), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH ×2, both isomers), 1.60- 1.17 (21H, m, lactam CH ×2 + chain (CH2)8 + CH3, both isomers), 1.14 (3H, s, CCH3, both isomers) and 0.84 (3H, t, J 7, CH2CHs, both isomers); δc (125 MHz, CDCl3) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH3)2), 42.1, 42.0 (NCH2), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (×4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH2), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH3).

8. 2 Steps



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 45 min, -78°C

1.2 18 h, -78°C → rt

1.3 R:NH_4Cl, S:H_2O, rt

2.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

2.2 S:H_2O, pH 2

Notes

1) reaction from p.46 in patent, 2) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.46 in patent, Reactants: 2, Reagents: 3, Solvents: 3, Steps: 2, Stages: 5, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

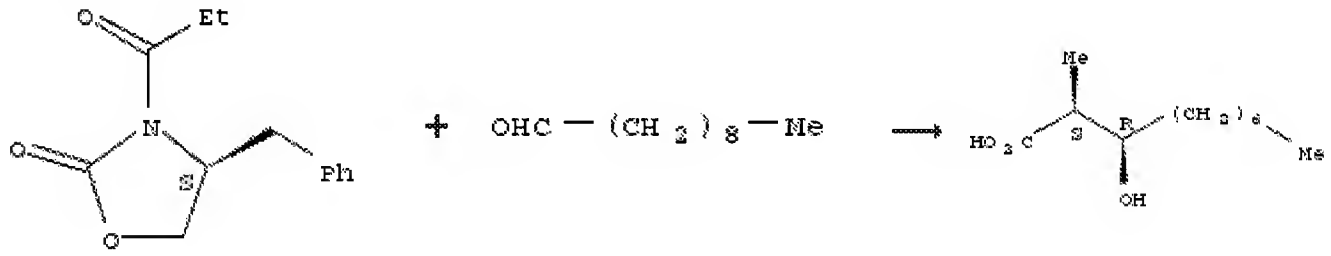
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at-78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacua and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4. The organic layer was dried over Na2SO4 and the solvent was removed to give methyl 2,2- dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δH (400 MHz, CDCl3) 3.70 (3H, s, OCH3), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH2)8), 1.19 (3H, s, CCH3), 1.17 (3H, s, CCH3) and 0.88 (3H, t, J 7 , CH2CH3) (no OH observed).

Step 2
Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and extracted with diethyl ether. The solution was dried over Na2SO4 and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 C; δH (400 MHz, CDCl3) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH2)8 + C(CH3)2) and 0.88 (3H, t, J7, CH2CH3).

9. 2 Steps



Overview

Steps/Stages

1.1 R:$TiCl_4$, S:CH_2Cl_2, rt → -20°C; 15 min, -20°C

1.2 R:EtN(Pr-i)$_2$, 40 min

1.3 R:NMP, 10 min

1.4 1 h

2.1 R:LiOH, R:H_2O_2, S:H_2O, S:THF, 18 h, rt

2.2 S:H_2O, rt, pH 2

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.43 in patent, 2) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.44 in patent, Reactants: 2, Reagents: 5, Solvents: 3, Steps: 2, Stages: 6, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Granger, David John, Fox, David John

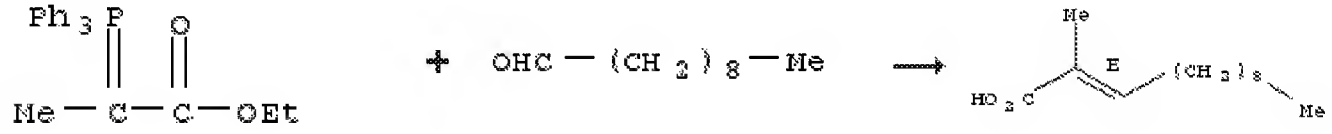
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin- 2-one (Intermediate) This aldol reaction was performed according to published method (Crimm·i·ns M.T; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH2Cl2 (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and TiCl4 (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methyl-pyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4). The organic layer was dried over Na2SO4 and reduced in vacuo. The crude product was chromatographed on silica ge1(10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoy1)-oxazolidin-2-one as an oil (1.34 g, 69%); (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoy1)-oxazolidin-2-one, yield (1.34 g, 69%); νmax/cm-1 1778 (NCO2), 1697 (CON); δH (500 MHz, CDCl3) 7.35-7.30 (2H, m, meta-Ph), 7.29-7.24 (1H, m,para-Ph), 7.21-7.17 (2H, m, ortho-Ph), 4.69 (1H, ddt, J 9.5, 7.5, 3.5, CHN), 4.21 (1H, t, J 9, OCHH), 4.17 (1H, dd, J 9, 3, OCHH), 3.93 (1H, ddd, J7, 4.5, 3, CHOH), 3.75 (1H, qd, J7, 2.5, CHCH3), 3.24 (1H, dd, J13.5, 3.5, CHHPh), 2.87 (1H, br s, CHOH), 2.78 (1H, dd, J13.5, 9.5, CHHPh), 1.56-1.20 (19H, m, (CH2)s + CHCH3) and 0.86 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 177.6 (CCO), 153.0 (OCO), 135.0 (ipso-Ph), 129.4, 129.0 (ortho- + meta- Ph), 127.4 (para- Ph), 71.5 (CHOH), 66.1 (OCH2), 55.1 (NCH), 42.1 (CHCH3), 37.8, 33.8, 31.9, 29.6 (x3), 29.3, 26.0, 22.7 (CH2), 14.1 and 10.3 (CH3); m/z (MH+ C23H36NO4 requires 390.2644) 390.2641.

Step 2
Example 53: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (1.42 mmol) was dissolved in THF (10 m1). Water (2 ml), aqueous hydrogen peroxide (8M, 0.5 mmol) and LiOH.H2O (3 mmol) were added, and the reaction was stirred for 18 hours. Na2SO3 (10 mmol) was added and the reaction was extracted with ethyl acetate. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4/0.5 M NaHSO4), and extracted with diethyl ether. The diethyl ether layer was dried over Na2SO4 and reduced in vacuo to give crude (2S,3R)-3-hydroxy-2-methyldecanoic acid; This material was used directly in the synthesis of (3S,2'S,3'R)-3-(3,-hydroxy-2'-methyldecanoyl)amino-caprolactam. (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) δH (400 MHz, CDCl3) 3.96-3.89 (1H, m, CHOH), 2.59 (1H, dq, J7, 3, CHCH3), 1.54- 1.36 (2H, m, CH,), 1.36-1.22 (14H, m, (CH3)2) and 1.20 (3H, d, J7, CHCH,).

10. 2 Steps



Overview

Steps/Stages

1.1 S:CH_2Cl_2, 18 h, rt

2.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

2.2 R:HCl, S:H_2O, acidify

Notes

1) stereoselective, reaction from p.41 in patent, 2) reaction from p.42 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

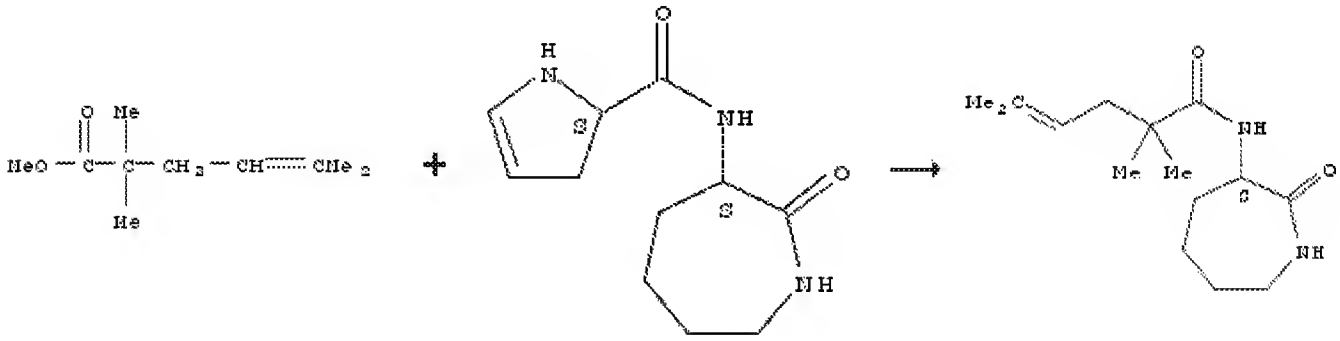
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
Example 46: (E)-Ethyl 2-methyldodec-2-enoate (Intermediate). Decanal (5 mmol) and (carbethoxyethylidene)triphenylphosphorane (10 mmol) were dissolved in CH2Cl2 (20 ml)and the reaction was stirred for 18 hours. The solvent was then removed in vacua and the residue was filter through a plug of silica gel with the aid of 5% diethyl ether in hexanes. The collected eluent was reduced in vacua to give (E)-ethyl 2-methyldodec-2-enoate as an oil (1.02 g, 88%). (E)-Ethyl 2-methyldodec-2-enoate, Yield (1.02 g, 88%). vmax/cm-1 1709 (CO), 1651 (C=C); δH (500 MHz, CDCl3) 6.73 (1H, tq, J7.5, 1.5, CH=C), 4.16 (2H, q, J 7 , OCH2), 2.13 (2H, br q, J7.5, CH2CH=C), 1.80 (3H, d, J 1.5, CH3C=CH), 1.45-1.37 (2H, m, chain CH2), 1.32-1.19 (15H, m, (CH2)6 + OCH2CH3) and 0.85 (3H, t, J 7 , (CH2)8CH3); δC (125 MHz, CDCl3) 168.3 (CO), 142.4 (CH=C), 127.6 (CH=C), 60.3 (OCH2), 31.8, 29.5, 29.4 (x2), 29.3, 28.6,28.5, 22.6 (CH2), 14.3, 14.1 and 12.3 (CH3); m/z (MH+ C15H29O2 requires 241.2168) 241.2165.

Step 2
Example 47: (E)-2-Methyldodec-2-enoic acid (Intermediate). (E)-Ethyl 2-methyldodec-2-enoate (1.43 mmol) was dissolved in ethanol (10 ml), and KOH (10 mmol) in water (5 ml) was added. The reaction was heated at reflux for 18 hours and then cooled. The solvent was removed in vacua and the residue partitioned between water and hexane. The aqueous layer was acidified with aqueous HCl, and was extracted with diethyl ether. The diethyl ether layer was dried over Na2SO4 and reduced in vacua to give (E)-2-methyldodec-2-enoic acid as a solid (308 mg, >95%) (E)-2-Methyldodec-2-enoic acid (Intermediate), Yield (308 mg, >95%). m.p. 28-31 °C; δH (400 MHz, CDCl3) 6.91 (1H, tq, 77.5, 1.5, CH=C), 2.18 (2H, br q, J7.5, CH2CH=C), 1.82 (3H, d, J1.5, CH3C=CH) , 1.48-1.39 (2H, m, chain CH2), 1.36-1.19 (12H, m, (CH2)6) and 0.88 (3H, t, J 7 , (CH2)8CH3) (no OH peak observed).

11. 2 Steps



[Step 2.1]

Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

2.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.38 in patent, 2) reaction from p.30 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

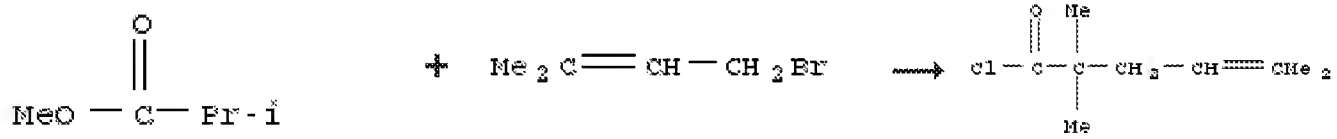
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

Step 2
Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; vmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

12. 2 Steps



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

2.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 4, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

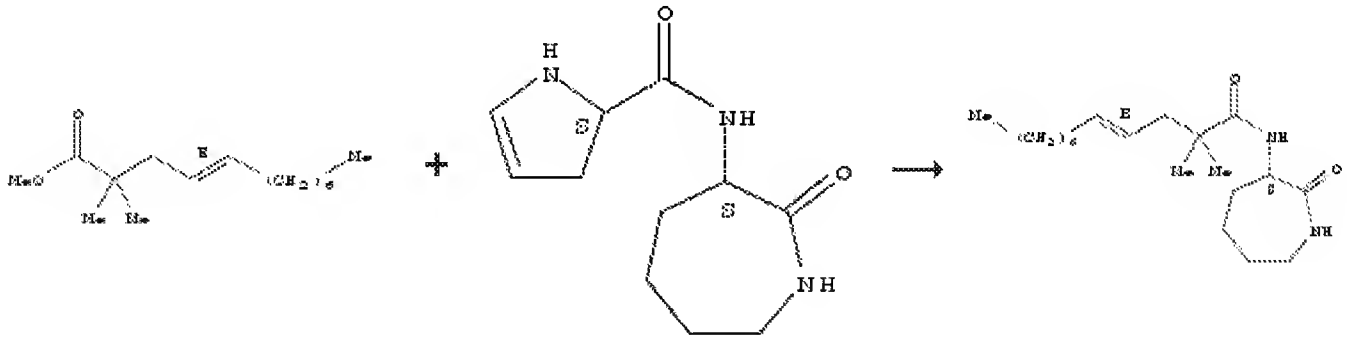
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N2. The reaction was stirred at - 78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) and hexane (3 x 250 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). νmax/cm-11732 (CO); δH (400 MHz, CDCl3) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH3), 2.20 (2H, d, J7.5, CHCH2, 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH3)2CO); δC (125 MHz, CDCl3) 178.4 (CO), 134.1 (Me2OCH), 119.8 (Me2C=CH), 51.6 (OCH3), 42.8 (Me2CCO), 38.7 (CH2), 25.9, 24.7 (x 2), 17.8 (CCH3); m/z (MH+ C10H19O2 requires 171.1385) 171.1388.

Step 2
2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

13. 2 Steps



[Step 2.1]

Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

2.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.29 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

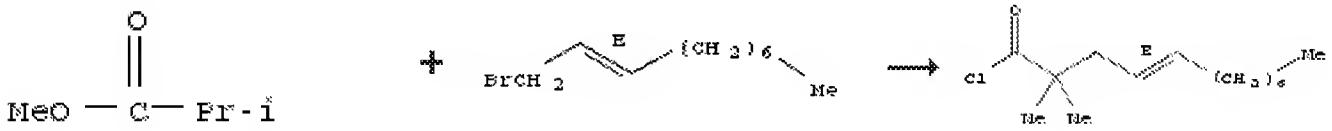
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the ether solvent removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (JE)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride**

Step 2
Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na2CO3 (3 0 mmol) in water (3 0 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). [α]25D (c = 1, CHCl3 +21.6; νmax/cm-1 3264 (NH), 1639 (CO), 1497 (NH); δH (500 MHz, CDCl3) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH2NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30- 3.17 (2H, m, CH2NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH2), 2.14 (1H, dd, 13.5, 7, CH=CHCH2), 2.01-1.87 (4H, br m, ring CH x2, + CH2CH=CH), 1.87-1.'74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH2)3) 1.1 3 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH2), 42.1 (x2)(CH2+ CMe2), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH2), 25.0, 24.8 (CH3) and 22.6 (CH3); m/z (MH+ C20H37N2O2 requires 337.2855) 337.2858.

14. 2 Steps



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

2.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

Notes

1) reaction from p.36 in patent, 2) reaction from p.37 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 4, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

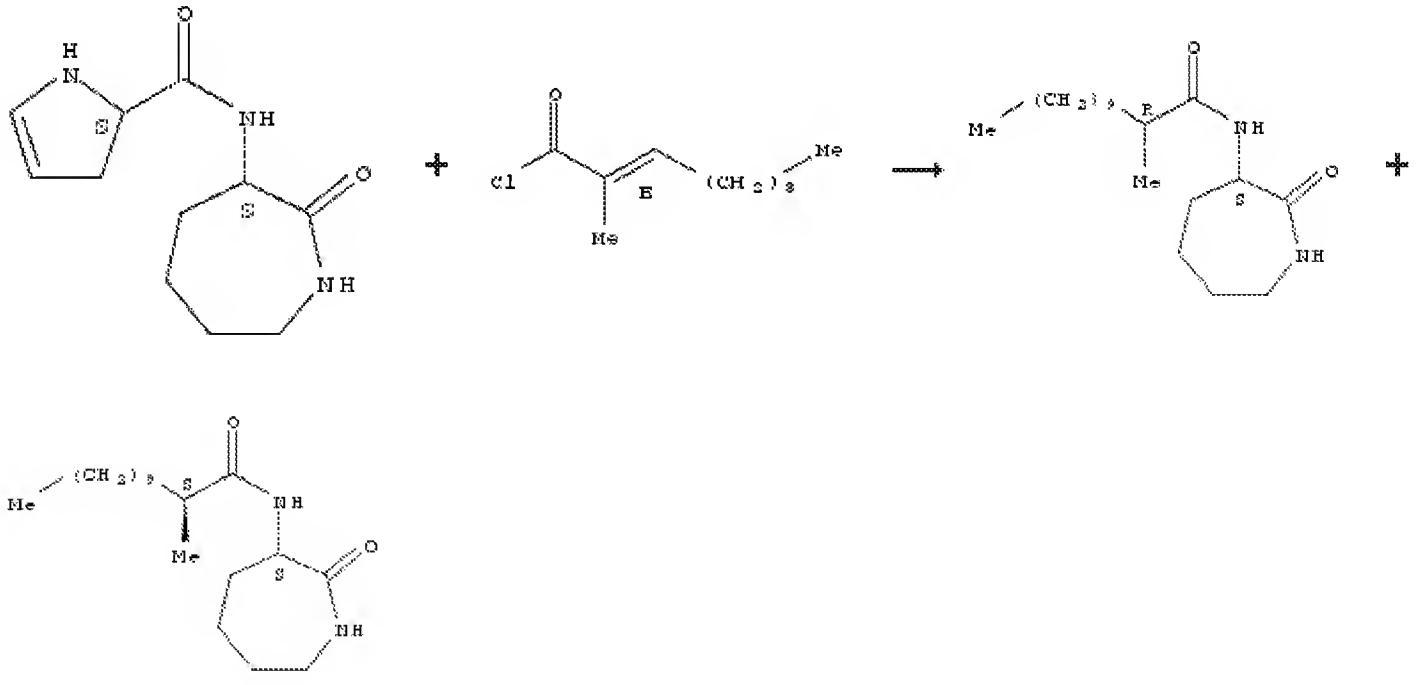
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1
(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N2. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacua, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). νmax/cm-1 1734 (CO); δH (400 MHz, CDCl3) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dtt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH3), 2.18 (2H, dd, J7, 1, CH2CMe2), 1.96 (2H, br q, J6.5, CH2CH2CH=CH), 1.35-1.20 (10H, m, (CH2)sCH3), 1.14 (6H, s, C(CH3)2), 0.87 (3H, t, J 6.5, CH2CH3) δc (125 MHz, CDCl3) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH3), 43.6 (CH2), 42.6 (Me2CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH2), 24.7 (C(CH3) × 2), 22.6 (CH2), 14.1 (CH2CH3); m/z (MH+ C15H29N2O2 requires 241.2168) 241.2169.

Step 2
(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the ether solvent removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (JE)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride**

15. 2 Steps



Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

2.1 R:H_2, C:$Pd(OH)_2$, S:MeOH, 18 h, rt

1) reaction from p.42 in patent, 2) stereoselective, overall yield is greater than 95%, reaction from p.43 in patent, Reactants: 2, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

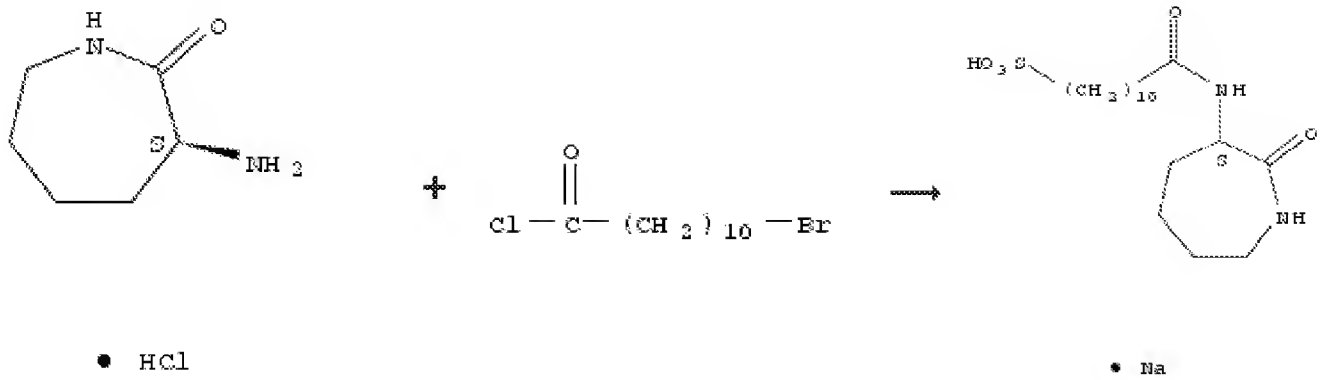
Step 1

Example 49: (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na2CO3 (6 mmol) in water (15 ml) were added to a solution of (E)-2-methyldodec-2-enoyl chloride (1.43 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was recrystallised from hexane to give (5)-(E)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam (297 mg, 65%). (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam, Yield (297 mg, 65%). m.p. (hexanes) 99-100 °C; vmax/cm-1 3282 (NH), 1656,1622 (CO and C=C), 1497 (NH); [α]25D (c = 1, CHCl3) +38.2; 5H (500 MHz, CDCl3) 7.15 (1H, d, J5.5, NHCH), 6.48-6.35 (2H, m, NHCH2 + CH=C), 4.54 (1H, ddd, J11, 5.5, 1.5, NHCH), 3.33-3.17 (2H, m, CHNH), 2.14-2.05 (3H, m, CH2CH=C + lactam ring CH), 2.02-1.93 (1H, m, lactam ring CH), 1.88-1.77 (5H,m, lactam ring CH x2 + CH3C=CH), 1.47-1.31 (4H, brm, lactam ring CH x2 + chain CH2), 1.31-1.17 (12H, m, (CH2)6) and 0.85 (3H, t, J7, CH2CH3); δC (125 MHz, CDCl3) 175.9,168.2 (CO), 136.9 (CH=C), 130.2 (CH=C, 52.3 (NHCH), 42.2 (NHCH2), 31.8, 31.6, 29.5, 29.4 (x2), 29.3, 28.9,28.7, 28.3, 27.9, 22.6 (CH2), 14.1 and 12.4 (CH3).

Step 2

Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2,-Methyldodecanoyl)amino-caprolactam: (5)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam (0.5 mmol) and Pd(OH)2 (20% on carbon) were added to methanol (10 ml) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of hydrogen. The reaction was then filtered, and the solvent removed in vacuo to give (3S,2R) and (3S',2'S)-3-(2'-methyldodecanoyl)amino-caprolactam as a solid (160 mg, >95%). Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2,-Methyldodecanoyl)amino-caprolactam, Yield (160 mg, >95%). νmax/cm-1 3313 (NH), 1671, 1636 (CO), 1515 (NH); δH (500 MHz, CDCl3) 6.91 (2H, d, J 5.5, CHNH, both isomers), 6.55 (2H, br s, CH2NH, both isomers), 4.57-4.47 (2H, m, CHNH, both isomers), 3.34-3.18 (4H, m, CH2NH, both isomers), 2.29-2.14 (2H, CH3CHCO, both isomers), 2.07 (2H, br d, J13.5, lactam ring CH, both isomers), 2.02-1.94 (2H, m, lactam ring CH, both isomers), 1.89-1.76 (4H, m, lactam ring CH x2, both isomers), 1.67-1.57 (2H, m, chain CH, both isomers), 1.51-1.33 (6H, m, lactam ring CH ×2 + side chain CH2, both isomers), 1.32-1.18 (32H, m, (CH2)8, both isomers), 1.13 (3H, d, J 7, CHCH3, one isomer), 1.11 (3H, d, J7, CHCH,, one isomer) and 0.87 (6H, t, J7.5, CH3, both isomers); δc (125 MHz, CDCl3) 175.9 (×2), 175.8 (×2)(CO, both isomers), 52.0, 51.9 (NCH), 42.1 (x2) (NCH2, both isomers), 41.3, 41.2 (CHCH3), 34.5, 34.1, 31.9 (x2), 31.8, 31.7, 29.6 (×6), 29.5 (×2), 29.3 (×2), 28.9 (×2), 28.0, 27.9, 27.4 (×2), 22.6 (×2) (CH2) 17.8, 17.6 and 14.1 (×2) (CH3); m/z (MH+ C19H37N2O2 requires 325.2855) 325.2858.

16. 2 Steps



• HCl

• Na

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 4 h, rt

2.1 R:Na_2SO_3, S:H_2O, S:EtOH, 14 h, reflux; cooled

Notes

1) reaction from p.31 in patent, 2) reaction from p.32 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

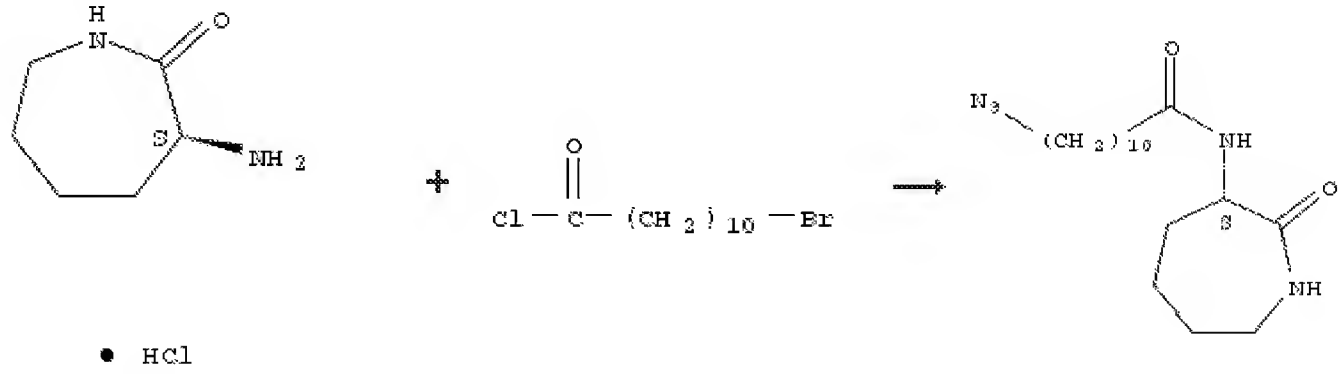
Step 1

Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na2CO3 (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]25D (c = 1, CHCl3) +31.8; νmax/cm-1 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δH (500 MHz, d6-DMSO) 7.76 (1H, t, J6.5, CH2NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J11, 7, CHNH), 3.51 (2H, t, J6.5, CH2Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 7, CHHNH), 2.17-2.06 (2H, m, CH2CONH), 1.85 (1H, dt, J14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH2CH2Br), 1.62 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br qn J6.5, CH2CH2CONH), 1.41-1.31 (3H, m, C-4 H and chain CH2) and 1.31-1.13 (11H, m, (CH2)8 + C-6 H); δc (125 MHz, d6-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH2), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH2); m/z (MH+ BrC17H32N2O2 requires 375.1647) 375.1655.

Step 2

Example 27: (5) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate: sodium sulfite (630 mg, 5 mmol) in water (3 ml) was added to (1S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in ethanol (2 ml) and the mixture was heated at reflux for 14 hours. The cooled reaction mixture was then added to ethanol (25 ml) and the reaction was filtered. The solvent was then removed in vacuo to give (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate (456 mg, 97%) (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate, Yield (456 mg, 97%). m.p. (EtOAc) 208-210 °C; [α]D25 (c = 1, H2O) -15.5; νmax/cm-1 3430, 3344, 3289 (NH + H2O), 1667, 1643 (CO), 1530 (NH) 1195, 1183 (SO3, asymm.), 1064 (SO3, symm.); δH (500 MHz, d6-DMSO) 7.76 (1H, t, J 6, CH2NH), 7.70 (1H, d, J7, CHNH), 4.35 (1H, dd, J10, 7.5, CHNH), 3.42 (8H, s, 4 × H2O) 3.17-3.00 (2H, m, CH2NH), 2.47-2.38 (2H, m, CH2SO3), 2.17-2.05 (2H, m, CH2CONH), 1.82 (1H, br s, J13.5, C-5 H), 1.75-1.66 (2H, m, C-4 H, C-6 H), 1.65- 1.50 (3H, m, C-5 H + chain CH2), 1.47-1.40 (2H, m, chain CH2) 1.35 (1H, qd, J13, 3, C-4 H), and 1.30-1.11 (13H, m, (CH2), + C-6 H); Sc (125 MHz, d6-DMSO) 174.5 (CO-ring), 171.5 (CO-chain), 51.6 (CH2SO3), 51.4 (NHCHCO), 40.8 (NCH2), 35.3, 31.3, 29.1 (×3), 29.0 (x2), 28.8, 28.6, 27.8, 25.5 and 25.1 (CH2); m/z MNa+ C17H31N2O5SNa2 requires 421.1749) 421.1748.

17. 2 Steps



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 4 h, rt

2.1 R:NaN_3, S:DMF, 14 h, 60°C

Notes

1) reaction from p.31 in patent, 2) reaction from p.31 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

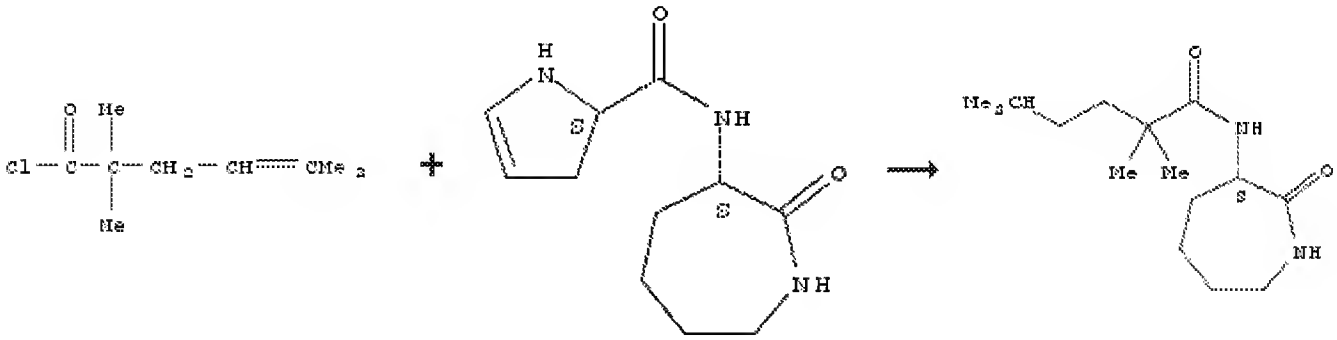
Experimental Procedure

Step 1

Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na2CO3 (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]25D (c = 1, CHCl3) +31.8; vmax/cm-1 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δH (500 MHz, d6-DMSO) 7.76 (1H, t, J6.5, CH2NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J11, 7, CHNH), 3.51 (2H, t, J6.5, CH2Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 7, CHHNH), 2.17-2.06 (2H, m, CH2CONH), 1.85 (1H, dt, J14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH2CH2Br), 1.62 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br qn J6.5, CH2CH2CONH), 1.41-1.31 (3H, m, C-4 H and chain CH2) and 1.31-1.13 (11H, m, (CH2)8 + C-6 H); δc (125 MHz, d6-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH2), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH2); m/z (MH+ BrC17H32N2O2 requires 375.1647) 375.1655.

Step 2
Example 26: (S)-3-(11'-azido-undecanoyl)amino-caprolactam: Sodium azide (650 mg, 10 mmol) was added to (S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in DMF (2 ml) and the mixture was heated at 60 °C for 14 hours. The solvent was then removed in vacuo and the residue was partitioned between water (20 ml) and EtOAc (3 x 20 ml). The combined organic layers were washed with 1M HCl aq (2 x 20 ml) and then dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (5)-3-(11'-azido-undecanoyl)amino-caprolactam (221 mg, 66%). (S)-3-(11'-azido-undecanoyl)amino-caprolactam, Yield (221 mg, 66%). m.p. (EtOAc) 71-72 °C; [α]25D (c= 1, CHCl3) +34.7; vmax/cm-1 3344, 3289 (NH), 2101 (N3) 1668, 1631 (CO), 1516 (NH); δH (500 MHz, d6-DMSO) 7.77 (1H, t, J 6, CH2NH), 7.67 (1H, d, J7, CHNH), 4.38 (1H, dd, J l1, 7, CHNH), 3.30 (2H, t, J 7, CH2N3), 3.15 (1H, ddd, J15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 5.5, CHHNH), 2.17-2.07 (2H, m, CH2CONH), 1.85 (1H, dt, J14, 3.5, C-5 H), 1.82-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, qt, J 13, 3.5, C-5 H), 1.51 (4H, m, CH2CH2CONH and CH2CH2N3), 1.36 (1H, qd, J13, 3, C-4 H), and 1.33-1.13 (13H, m, (CH2)6 + C-6 H); δc (125 MHz, d6-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 50.7 (CH2N3), 40.7 (NCH2), 35.3, 31.3, 29.0 (×2), 28.9, 28.7, 28.6, 28.3, 27.8, 26.2 and 25.4 (CH2); m/z (MNa+ C17H31N2O2Na requires 360.2375) 360.2360.

18. 2 Steps



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

2.1 R:H_2, C:$Pd(OH)_2$, S:AcOEt, 14 h, rt

Notes

1) reaction from p.30 in patent, 2) reaction from p.30 in patent, Reactants: 2, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Gmainger, David John, Fox, David John

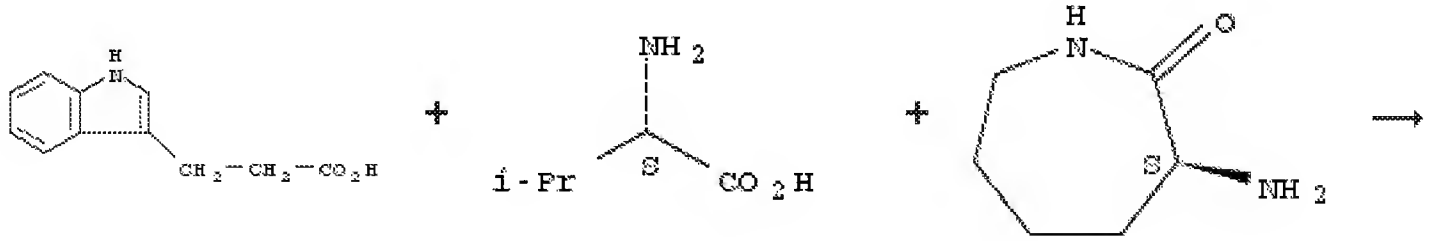
From PCT Int. Appl., 2005053702, 16 Jun 2005

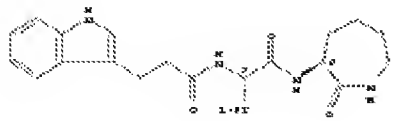
Experimental Procedure

Step 1
Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; νmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

Step 2
Example 24: (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmostsphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (6)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]25D (c=1, CHCl3) +27.8; νmax/cm-1 3249 (NH), 1654, 1638 (CO), 1502 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5.0, CHNH), 6.75-6.55 (1H, br m, CH2NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH2 + CH(CH3)2), 1.13 (3H, s, CH3), 1.12 (3H, 8, CH3), 1.08-1.02 (2H, m, CH2), 0.82 (3H, s, CH3), 0.80 (3H, s, CH3); δc (125 MHz, CDCl3) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH2N), 41.9 (CH2CMe2), 39.0, 33.7, 31.5, 28.9 (CH2), 28.4 (Me2CH), 27.9 (CH2), 25.3, 25.2, 22.6, 22.5 (CH3); m/z (MH+ C15H29N2O2 requires 269.2229) 269.2219.

19. Single Step





96%

Overview

Steps/Stages **Notes**

1) solid-supported reaction, solid-phase automated peptide synthesizer used, reaction from p.36 in patent, Reactants: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

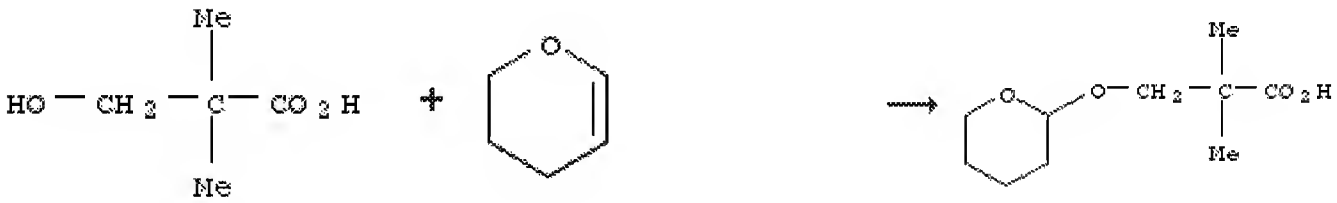
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 34: (S)-aminocaprolactam-(L)-valine-(TL)-Desaminotryptophan. This tripeptide was made on a solid-phase automated peptide synthesiser using (S)-aminocaprolactam for the final peptide coupling step. Mr(Calc) = 398.4600. Observed Mr by mass spectrometry 398.3. Purity (%TIC in molecular ion peak) = 96% **(S)-aminocaprolactam-(L)-valine-(TL)-Desaminotryptophan**

20. Single Step



95%

Overview

Steps/Stages

1.1 R:p-$MeC_6H_4SO_3H$, S:CH_2Cl_2, 3 h, rt

1.2 R:KOH, S:H_2O, S:EtOH, 18 h, reflux

1.3 S:H_2O, pH 2

Notes

1) regioselective in stage 1, Na2SO4/NaHSO4 buffer used in stage 3, reaction from p.47 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

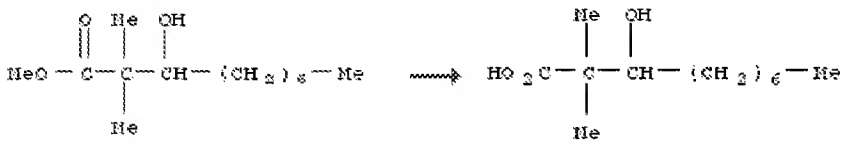
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 60: 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (Intermediate) 2,2-Dimethyl-3-hydroxy propionic acid (100 mmol) and 3,4-dihydro-2H-pyran (210 mmol) were dissolved in dichloromethane (50 ml), and para-toluenesulfonic acid (10 mg) was added and the reaction was stirred at ambient temperature for 3 hours. The reaction solvent was then removed and the residue was dissolved in ethanol (100 ml). A solution of KOH (120 mmol) in water (30 ml) was added and the reaction was heated at reflux for 18 hours. The reaction solvent was removed in vacua and the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4) and then extracted with diethyl ether. The diethyl ether layer was then dried over Na2SO4 and the solvent was removed in vacuo to give 2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid as an oil (20.0 g, >95%). 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propiomc acid, Yield (20.0 g, >95%). δH (400 MHz, CDCl3) 4.62 (1H, t, J 3.5, CHO2), 3.82 (1H, ddd, J 12, 9, 3, ring CH2O), 3.75 (1H, d, J 12, chain CH2O), 3.55-3.46 (1H, m, ring CH2O), 3.40 (1H, d, J 12, chain CH2O), 1.90-1.45 (6H, m, (CH2)3), 1.25 (3H, s, CH3) and 1.23 (3H, s, CH3).

21. Single Step



Overview

Steps/Stages

1.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

1.2 S:H_2O, pH 2

Notes

1) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.46 in patent, Reactants: 1, Reagents: 1, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

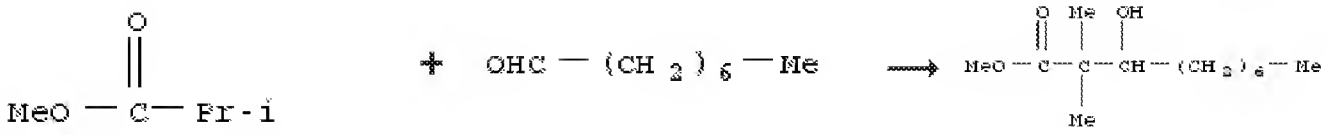
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and extracted with diethyl ether. The solution was dried over Na2SO4 and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 C; δH (400 MHz, CDCl3) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH2)8 + C(CH3)2) and 0.88 (3H, t, J7, CH2CH3).

22. Single Step



77%

Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 45 min, -78°C

1.2 18 h, -78°C → rt

1.3 R:NH_4Cl, S:H_2O, rt

Notes

1) reaction from p.46 in patent, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

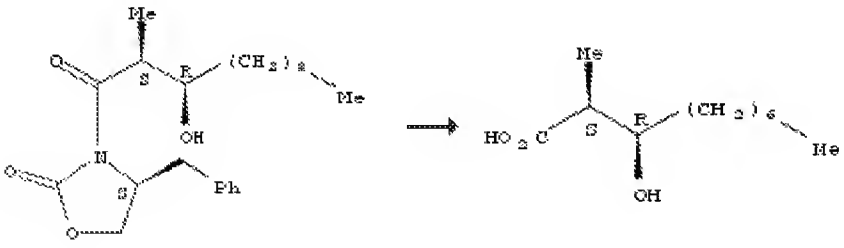
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at-78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacua and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4. The organic layer was dried over Na2SO4 and the solvent was removed to give methyl 2,2- dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δH (400 MHz, CDCl3) 3.70 (3H, s, OCH3), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH2)8), 1.19 (3H, s, CCH3), 1.17 (3H, s, CCH3) and 0.88 (3H, t, J 7 , CH2CH3) (no OH observed).

23. Single Step



Overview

Steps/Stages

Notes

1.1 R:LiOH, R:H_2O_2, S:H_2O, S:THF, 18 h, rt

1.2 S:H_2O, rt, pH 2

1) Na2SO4/NaHSO4 buffer used in stage 2, reaction from p.44 in patent, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

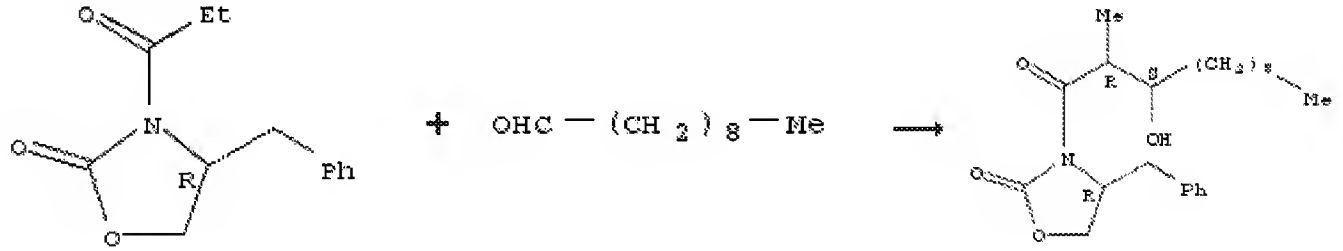
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 53: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (1.42 mmol) was dissolved in THF (10 m1). Water (2 ml), aqueous hydrogen peroxide (8M, 0.5 mmol) and LiOH.H2O (3 mmol) were added, and the reaction was stirred for 18 hours. Na2SO3 (10 mmol) was added and the reaction was extracted with ethyl acetate. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na2SO4/0.5 M NaHSO4), and extracted with diethyl ether. The diethyl ether layer was dried over Na2SO4 and reduced in vacuo to give crude (2S,3R)-3-hydroxy-2-methyldecanoic acid; This material was used directly in the synthesis of (3S,2'S,3'R)-3-(3,-hydroxy-2'-methyldecanoyl)amino-caprolactam. (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) δH (400 MHz, CDCl3) 3.96-3.89 (1H, m, CHOH), 2.59 (1H, dq, J7, 3, CHCH3), 1.54- 1.36 (2H, m, CH,), 1.36-1.22 (14H, m, (CH3)2) and 1.20 (3H, d, J7, CHCH,).

24. Single Step



Overview

Steps/Stages

1.1 R:$TiCl_4$, S:CH_2Cl_2, rt → -20°C; 15 min, -20°C

1.2 R:$TiCl_4$, 40 min

1.3 R:NMP, 10 min

1.4 1 h

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.44 in patent, Reactants: 2, Reagents: 2, Solvents: 1, Steps: 1, Stages: 4, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

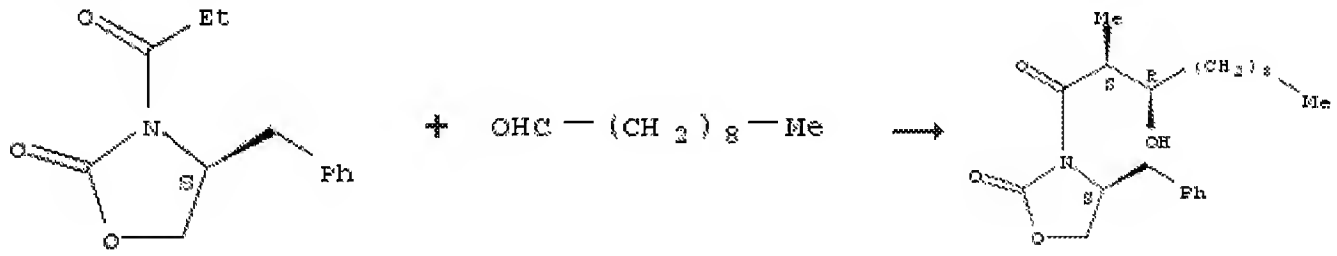
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

General/Typical Procedure: **Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin- 2-one (Intermediate)** This aldol reaction was performed according to published method (Crimm·i·ns M.T; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH_2Cl_2 (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and $TiCl_4$ (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methyl-pyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na_2SO_4 / 0.5 M $NaHSO_4$). The organic layer was dried over Na_2SO_4 and reduced in vacuo. The crude product was chromatographed on silica ge1(10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoy1)-oxazolidin-2-one as an oil (1.34 g, 69%); **Example 52: (4R,2'R,3'S)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin- 2-one (Intermediate)** (R)-4-Benzyl-3-propionyl-oxazolidin-2-one was converted into (4R,2'R,3'S)-4-benzyl- 3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one according to the above procedure. NMR spectroscopic data is identical. m/z (MH^+ $C_{23}H_{35}NO_4$ requires 390.2644) 390.2638.

25. Single Step



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Overview

Steps/Stages

1.1 R:$TiCl_4$, S:CH_2Cl_2, rt → -20°C; 15 min, -20°C

1.2 R:EtN(Pr-i)$_2$, 40 min

1.3 R:NMP, 10 min

1.4 1 h

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.43 in patent, Reactants: 2, Reagents: 3, Solvents: 1, Steps: 1, Stages: 4, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

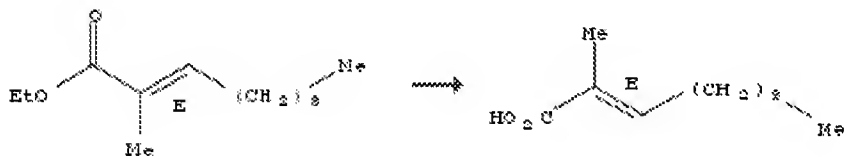
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin- 2-one (Intermediate) This aldol reaction was performed according to published method (Crimm·i·ns M.T; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH2Cl2 (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and TiCl4 (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methyl-pyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4). The organic layer was dried over Na2SO4 and reduced in vacuo. The crude product was chromatographed on silica ge1(10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoy1)-oxazolidin-2-one as an oil (1.34 g, 69%); (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoy1)-oxazolidin-2-one, yield (1.34 g, 69%); νmax/cm-1 1778 (NCO2), 1697 (CON); δH (500 MHz, CDCl3) 7.35-7.30 (2H, m, meta-Ph), 7.29-7.24 (1H, m,para-Ph), 7.21-7.17 (2H, m, ortho-Ph), 4.69 (1H, ddt, J 9.5, 7.5, 3.5, CHN), 4.21 (1H, t, J 9, OCHH), 4.17 (1H, dd, J 9, 3, OCHH), 3.93 (1H, ddd, J7, 4.5, 3, CHOH), 3.75 (1H, qd, J7, 2.5, CHCH3), 3.24 (1H, dd, J13.5, 3.5, CHHPh), 2.87 (1H, br s, CHOH), 2.78 (1H, dd, J13.5, 9.5, CHHPh), 1.56-1.20 (19H, m, (CH2)s + CHCH3) and 0.86 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 177.6 (CCO), 153.0 (OCO), 135.0 (ipso-Ph), 129.4, 129.0 (ortho- + meta- Ph), 127.4 (para- Ph), 71.5 (CHOH), 66.1 (OCH2), 55.1 (NCH), 42.1 (CHCH3), 37.8, 33.8, 31.9, 29.6 (x3), 29.3, 26.0, 22.7 (CH2), 14.1 and 10.3 (CH3); m/z (MH+ C23H36NO4 requires 390.2644) 390.2641.

26. Single Step



95%

Overview

Steps/Stages

1.1 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

1.2 R:HCl, S:H_2O, acidify

Notes

1) reaction from p.42 in patent, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

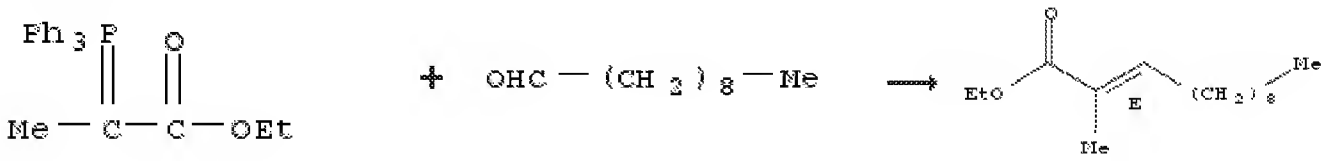
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 47: (E)-2-Methyldodec-2-enoic acid (Intermediate). (E)-Ethyl 2-methyldodec-2-enoate (1.43 mmol) was dissolved in ethanol (10 ml), and KOH (10 mmol) in water (5 ml) was added. The reaction was heated at reflux for 18 hours and then cooled. The solvent was removed in vacua and the residue partitioned between water and hexane. The aqueous layer was acidified with aqueous HCl, and was extracted with diethyl ether. The diethyl ether layer was dried over Na2SO4 and reduced in vacua to give (E)-2-methyldodec-2-enoic acid as a solid (308 mg, >95%) (E)-2-Methyldodec-2-enoic acid (Intermediate), Yield (308 mg, >95%). m.p. 28-31 °C; δH (400 MHz, CDCl3) 6.91 (1H, tq, 77.5, 1.5, CH=C), 2.18 (2H, br q, J7.5, CH2CH=C), 1.82 (3H, d, J1.5, CH3C=CH) , 1.48-1.39 (2H, m, chain CH2), 1.36-1.19 (12H, m, (CH2)6) and 0.88 (3H, t, J 7 , (CH2)8CH3) (no OH peak observed).

27. Single Step



88%

Overview

Steps/Stages

1.1 S:CH_2Cl_2, 18 h, rt

Notes

1) stereoselective, reaction from p.41 in patent, Reactants: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

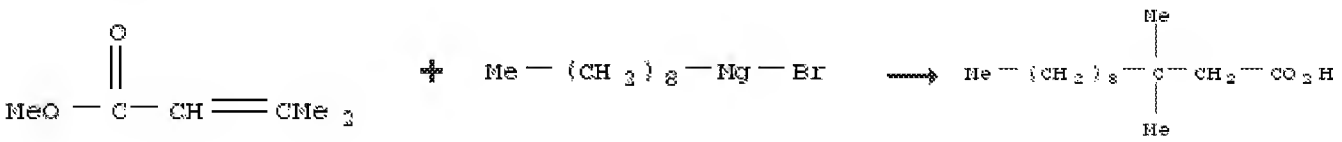
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 46: (E)-Ethyl 2-methyldodec-2-enoate (Intermediate). Decanal (5 mmol) and (carbethoxyethylidene)triphenylphosphorane (10 mmol) were dissolved in CH2Cl2 (20 ml)and the reaction was stirred for 18 hours. The solvent was then removed in vacua and the residue was filter through a plug of silica gel with the aid of 5% diethyl ether in hexanes. The collected eluent was reduced in vacua to give (E)-ethyl 2-methyldodec-2-enoate as an oil (1.02 g, 88%). (E)-Ethyl 2-methyldodec-2-enoate, Yield (1.02 g, 88%). vmax/cm-1 1709 (CO), 1651 (C=C); δH (500 MHz, CDCl3) 6.73 (1H, tq, J7.5, 1.5, CH=C), 4.16 (2H, q, J 7 , OCH2), 2.13 (2H, br q, J7.5, CH2CH=C), 1.80 (3H, d, J 1.5, CH3C=CH), 1.45-1.37 (2H, m, chain CH2), 1.32-1.19 (15H, m, (CH2)6 + OCH2CH3) and 0.85 (3H, t, J 7 , (CH2)8CH3); δC (125 MHz, CDCl3) 168.3 (CO), 142.4 (CH=C), 127.6 (CH=C), 60.3 (OCH2), 31.8, 29.5, 29.4 (x2), 29.3, 28.6,28.5, 22.6 (CH2), 14.3, 14.1 and 12.3 (CH3); m/z (MH+ C15H29O2 requires 241.2168) 241.2165.

28. Single Step



76%

Overview

Steps/Stages

Notes

1.1 R:Me_3SiCl, R:CuI, S:THF, rt → -15°C; 1 h, -15°C; overnight, -15°C → rt

1.2 R:NH_4Cl, S:H_2O, rt

1.3 R:KOH, S:H_2O, S:EtOH, 18 h, reflux; cooled

1.4 R:HCl, S:H_2O, pH 2

1) reaction from p.40 in patent, Reactants: 2, Reagents: 5, Solvents: 3, Steps: 1, Stages: 4, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

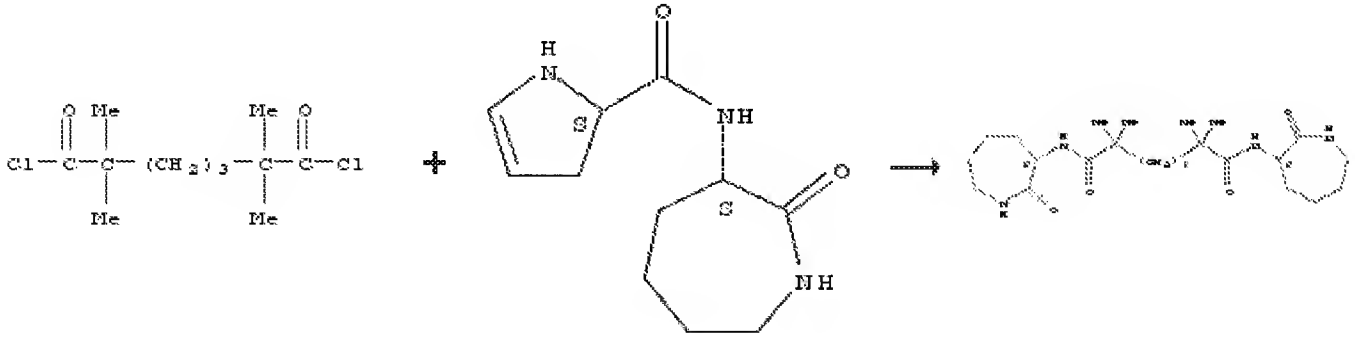
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 43: 3,3-Dimethyldodecanoic acid (Intermediate). CuI (2 mmol), trimethylsilyl chloride (24 mmol) and methyl 3,3-dimethylacrylate (20 mmol) in THF (25 mmol) was cooled to -15 °C, and a solution of nonylmagnesium bromide (24 mmol) in THF (80 ml) was added over one hour. The reaction was allowed to warm to room temperature overnight and it was then quenched by the addition of saturated aqueous ammonium chloride. The THF was removed in vacuo and the residue was partitioned between hexanes and water. The organic layer was reduced in vacuo and the crude methyl 3,3-dimethyldodecanoate was dissolved in ethanol (50 ml). KOH (100 mmol) in water (10 ml) was added and the reaction was heated at reflux for 18 hours. The reaction was then allowed to cool, and the solvent was removed in vacuo. and the residue was partitioned between hexane and water. The aqueous layer was then acidified to pH 2 with aqueous HCl. and extracted with diethyl ether. The ether layer was dried over Na2SO4 and the solution was then reduced in vacuo to give 3,3-dimethyldodecanoic acid as an oil (3.47 g, 76%). 3,3-Dimethyldodecanoic acid, Yield (3.47 g, 76%). νmax/cm-1 1702 (CO); δH (500 MHz, CDCl3) 11.12 (1H, br s, OH), 2.21 (2H, s, CH2CO); 1.32-1.20 (16H, m, (CH2)8), 1.00 (6H, s, C(CH3)2) and 0.87 (3H, t, J7, CH2CH3); δC (125 MHz, CDCl3) 179.1 (CO),45.9, 42.3 (CH2), 33.2 (C(CH3)2), 31.9, 30.3, 29.6 (x2), 29.3, 27.1 (x2) (C(CH3)2), 24.0, 22.6 (CH2) and 14.1 (CH3); m/z (M+ C14H28O2 requires 228.2089) 228.2082

29. Single Step



46%

Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.38 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

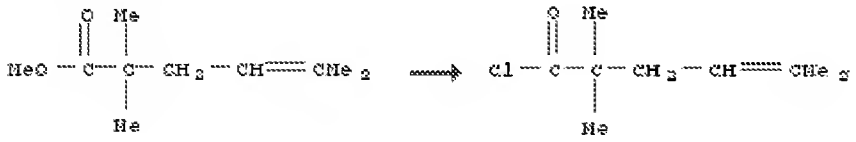
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(S,S) N,N'-bis-(2'-oxo-azepan-3'-yl) 2,2,6,6-tetramethylheptadiamide: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of 2,2,6,6-tetramethyl- heptandioyl dichloride (1 mmol)in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (3,3)-dimer (199 mg, 46%). Yield 199 mg, 46% m.p. 234-236 °C; [α]25D (c = 1, CHCl3) +29.4; νmax/cm-1 3379, 3255 (NH), 1683, 1637 (CO), 1507, 1497 (NH); δH (500 MHz, CDCl3) 7.07 (2H, d, J 5.5, CHNH), 6.42 (2H, br s, CH2NH), 4.44 (2H, ddd, J11, 5.5, 1.5, CHNH), 3.31- 3.17 (4H, m, CH2NH), 2.04-1.94 (4H, m, ring CH), 1.86-1.73 (4H, m, ring CH), 1.51-1.31 (8H, br m, 2 × ring CH + CH2CMe2) and 1.12 (14H, m, chain CH2CH2CH2 + CMe2); δc (125 MHz, CDCl3) 176.9, 175.9 (CO), 52.1 (NHCH), 42.0 (CMe2), 42.1, 41.5, 31.5, 28.9, 28.0 (CH2), 25.3, 25.1 (CH3) and 20.0 (CH2); m/z (M+ C23H40N4O4 requires 436.30496) 436.30437.

30. Single Step



Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

Notes

1) reaction from p.38 in patent, Reactants: 1, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

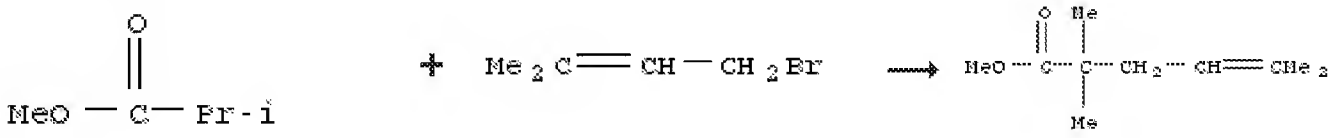
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) and diethyl ether (3x150 ml). The combined organic layers were dried over Na_2CO_3 and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

31. Single Step



81%

Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

Notes

1) reaction from p.37 in patent, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

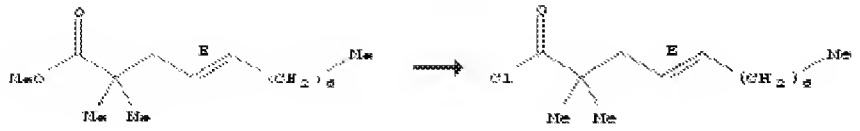
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N2. The reaction was stirred at - 78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) and hexane (3 x 250 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). νmax/cm-11732 (CO); δH (400 MHz, CDCl3) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH3), 2.20 (2H, d, J7.5, CHCH2, 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH3)2CO); δC (125 MHz, CDCl3) 178.4 (CO), 134.1 (Me2OCH), 119.8 (Me2C=CH), 51.6 (OCH3), 42.8 (Me2CCO), 38.7 (CH2), 25.9, 24.7 (x 2), 17.8 (CCH3); m/z (MH+ C10H19O2 requires 171.1385) 171.1388.

32. Single Step



Overview

Steps/Stages

1.1 R:NaOH, S:H_2O, S:EtOH, 6 h, reflux; cooled

1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH_2Cl_2, 1 h

Notes

1) reaction from p.37 in patent, Reactants: 1, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

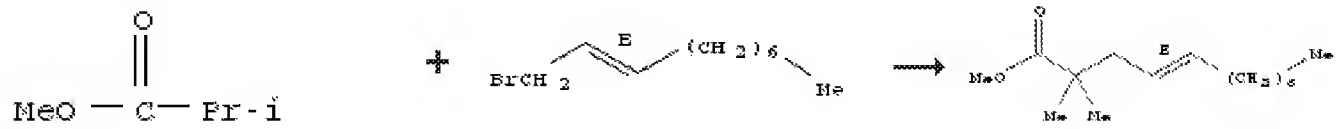
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M $NaHSO_4$ / 0.5 M Na_2SO_4) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the ether solvent removed *in vacuo* to give crude (*E*)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil, The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (JE)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(*E*)-2,2-Dimethyl-dodec-4-enoyl chloride**

33. Single Step



Overview

Steps/Stages

1.1 R:LiN(Pr-i)$_2$, S:THF, 1 h, -78°C

1.2 14 h, -78°C → rt

Notes

1) reaction from p.36 in patent, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

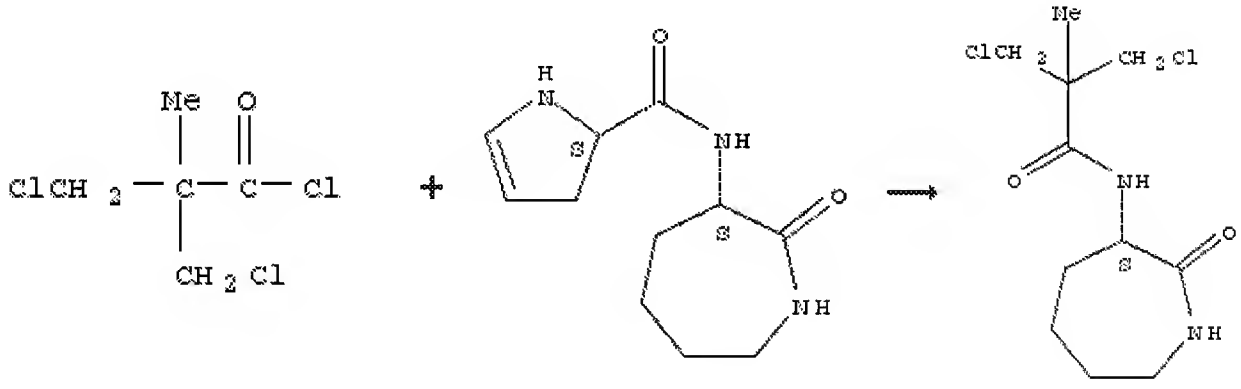
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N2. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacua, and the residure was partitioned between pH 2 aqueous buffer (0.5 M NaHSO4 / 0.5 M Na2SO4) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na2SO4 and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). νmax/cm-1 1734 (CO); δH (400 MHz, CDCl3) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dtt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH3), 2.18 (2H, dd, J7, 1, CH2CMe2), 1.96 (2H, br q, J6.5, CH2CH2CH=CH), 1.35-1.20 (10H, m, (CH2)sCH3), 1.14 (6H, s, C(CH3)2), 0.87 (3H, t, J 6.5, CH2CH3) δc (125 MHz, CDCl3) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH3), 43.6 (CH2), 42.6 (Me2CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH2), 24.7 (C(CH3) × 2), 22.6 (CH2), 14.1 (CH2CH3); m/z (MH+ C15H29N2O2 requires 241.2168) 241.2169.

34. Single Step



69%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.48 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

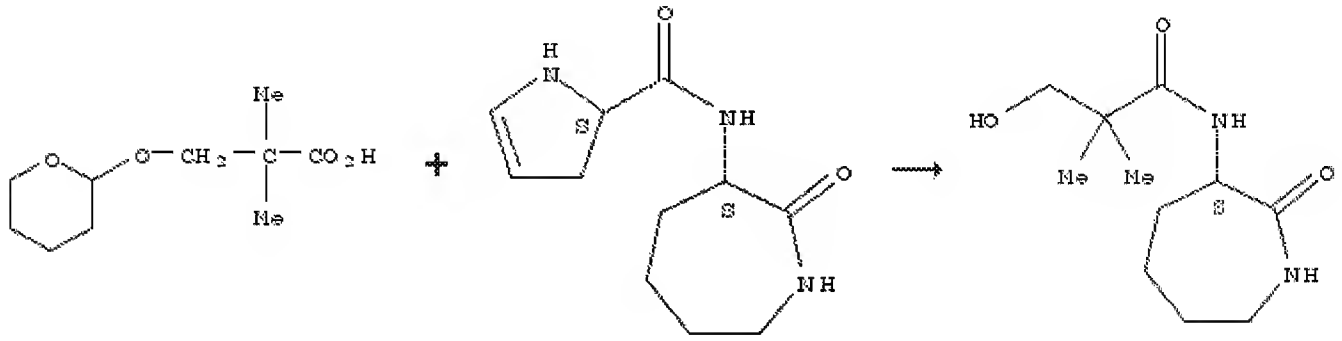
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 62: (S)-(3'-Chloro-2'-(chloromethyl)-2'-methylpropionyl)amino caprolactam. (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of 3,3'-dichloropivaloyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacua. The residue was recrystallised from hexane to give (S)-(3'-chloro-2'-(chloromethyl)-2'-methylpropionyl)amino-caprolactam (973 mg, 69%). (S)-(3'-Chloro-2'-(chloromethyl)-2'-methylpropionyl)amino caprolactam. Yield (973 mg, 69%). m.p. (hexanes) 95-96 °C; νmax/cm-1 (c = 0.5, CHCl2) +16.4; δH (500 MHz, CDCl3) 7.33 (1H, d, J 5.0, CHNH), 6.82-6.62 (1H, br m, CH2NH), 4.49 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.78 (1H, d, J11, CHHCl), 3.74 (1H, d, J 11, CHHCl), 3.69 (1H, d, J11, CHHCl), 3.66 (1H, d, J11, CHHCl), 3.29-3.17 (2H, m, CH2NH), 2.05 (1H, br s, J13.5, ring CH), 2.01-1.93 (1H, m, ring CH), 1.87-1.71 (2H, m, 2 × ring CH) and 1.49-1.31 (3H, m, 2 × ring CH + CH3); δc (125 MHz, CDCl3) 175.4, 170.6 (CO), 52.6 (NHCHCO), 49.1 (CCO), 48.7, 48.6 (CH2Cl), 42.1 (CH2N), 31.1, 28.8, 27.9 (CH2 lactam) and 18.9 (CH3).

35. Single Step



83%

Overview

Steps/Stages

1.1 R:1-Benzotriazolol, R:Diimidazolylketone, S:THF, 4 h, reflux; reflux → rt

1.2 R:Disodiumcarbonate, S:H_2O, 18 h, rt

1.3 R:AcCl, S:MeOH, 18 h, rt

Notes

1) reaction from p.48 in patent, Reactants: 2, Reagents: 4, Solvents: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

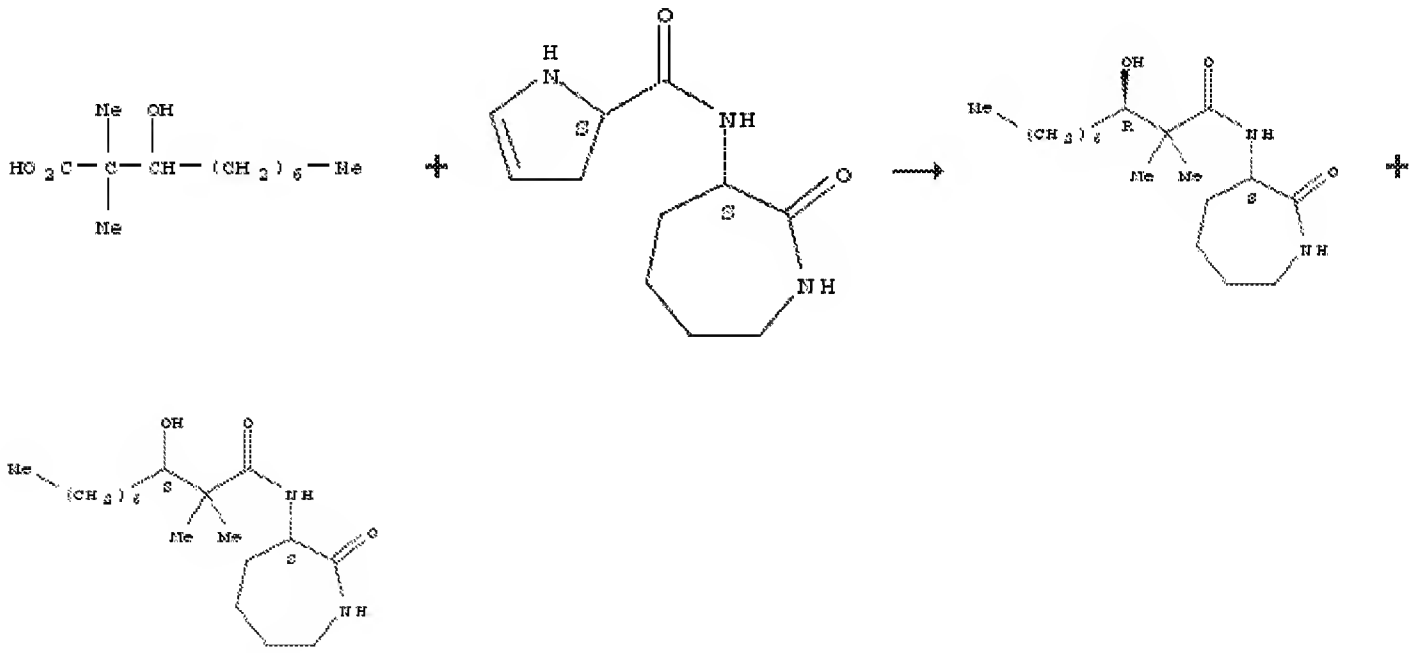
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 61: (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (4.65 mmol), 1-hydroxybenzotriazole monohydrate (4.65 mmol) and carbonyl diimidazole (4.50 mmol) were dissolved in THF (30 ml) and the reaction was heated at reflux for 4 hours. After the reaction was cooled to ambient temperature, a solution of(S,S)-3-amino- caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na2CO3 (15 mmol) in water (30 ml) was added and the reaction was stirred for 18 hours. The THF was then removed from the reaction by distillation in vacuo and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was dried over Na2SO4 and reduced in vacuo. The residue was dissolved in MeOH, and acetyl chloride (1 ml) was added. The reaction was stirred at ambient temperature for 18 hours, and then reduced in vacuo to give (S)- (2'-dimethyl-3'-hydroxy propionyl)amino-caprolactam as a solid (854 mg, 83%). (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam, Yield (854 mg, 83%). m.p. 97-99 °C; [α]25D (c = 0.5, CHCl3) +30.0; δH (400 MHz, CDCl3) 7.24 (1H, d, J 5.0, CHNH), 6.38 (1H, br s, CH2NH), 4.49 (1H, dd, J 10, 6, CHNH), 3.54 (1H, d, J 11, CHHOH), 3.49 (1H, d, J11, CHHOH), 3.33-3.20 (2H, m, CH2NH), 2.03-1.96 (2H, m, 2 × ring CH), 1.87-1.72 (2H, m, 2 × ring CH), 1.50-1.30 (2H, m, 2 × ring CH), 1.20 (3H, s, CH3) and 1.18 (3H, s, CH3); δc (125 MHz, CDCl3) 177.2, 176.0 (CO), 69.9 (CHOH), 52.1 (NHCHCO), 43.2 (CCO), 41.9 (CH2N), 31.1, 28.8, 27.9 (CH2 lactam), 22.4 and 22.3 (CH3).

36. Single Step



Overview

Steps/Stages

1.1 R:1-Benzotriazolol, R:EtN=C=N(CH$_2$)$_3$NMe$_2$•HCl, S:THF, 4 h, rt

1.2 R:Disodiumcarbonate, S:H$_2$O, 18 h, rt

Notes

1) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 2, Reagents: 3, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

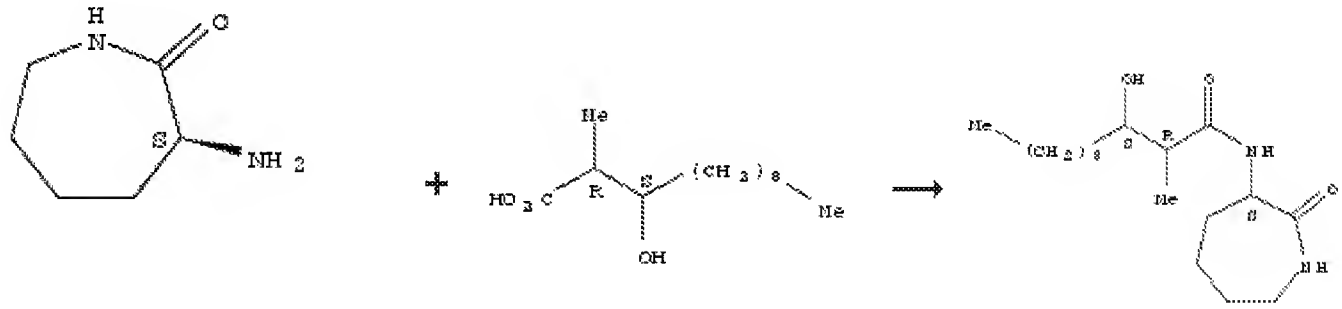
By Granger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na2CO3 (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na2SO4 / 0.5 M NaHSO4 and dilute aqueous sodium hydroxide, and then dried over Na2SO4 and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'- hydroxy-2',2'-dimethyldecanoyl)amino-caprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δH (500 MHz, CDCl3) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH2, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH2, both isomera), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH ×2, both isomers), 1.60- 1.17 (21H, m, lactam CH ×2 + chain (CH2)8 + CH3, both isomers), 1.14 (3H, s, CCH3, both isomers) and 0.84 (3H, t, J 7, CH2CHs, both isomers); δc (125 MHz, CDCl3) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH3)2), 42.1, 42.0 (NCH2), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (×4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH2), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH3).

37. Single Step



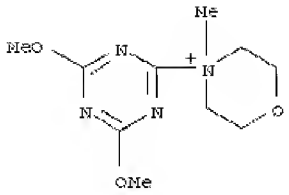
• HCl

18%

Overview

Steps/Stages **Notes**

1.1 R:



• Cl⁻

R:Et_3N,

S:MeOH, rt → 0°C; 4 h, 0°C

1) reaction from p.45 in patent, Reactants: 2, Reagents: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

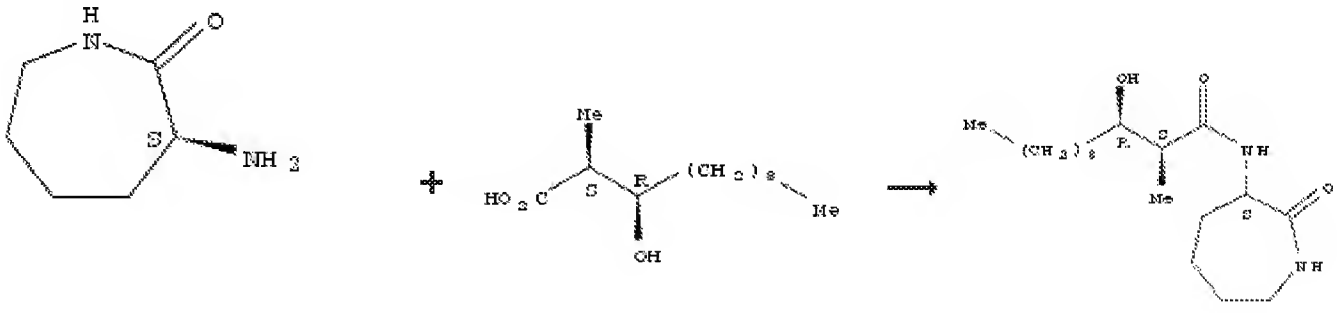
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 56: (3S,2'R,3'S)-3-(3'-Hydroxy-2'-methyldecanoyl)amino-caprolactam: (2R,3'S)-3-Hydroxy-2-methyldecanoic acid (1.40 mmol), (S)-3-amino-caprolactam hydrochloride (1.50 mmol), triethylamine (2 mmol), and 4-(4,6- dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride (1.40 mmol) were reacted together, as above to produce (3S,2'R,3'S)-3-(3'-hydroxy-2'- methyldecanoyl)amino-caprolactam which was recrystallised from ethyl acetate/hexane (86 mg, 18%) (3S,2'R,3'S)-3-(3'-Hydroxy-2'-methyldecanoyl)amino-caprolactam, Yield (86 mg, 18%). m.p. (hexanes) 118-121 °C; νmax/cm-1, 3294 (NH), 1667, 1613 (CO), 1533 (NH); [α]25D (c = 0.5, CHCl3) +14.8; δH (500 MHz, CDCl3) 7.11 (1H, d, J6, NHCH), 6.54 (1H, br s, NHCH2), 4.53 (1H, ddd, J 11, 6.5, 1.5, NCH), 3.87-3.80 (1H, m, CHOH), 3.70 (1H, br s, OH), 3.34-3.20 (2H, m, NCH2), 2.37 (1H, dq, J 7, 3, CHCH3), 2.11-1.96 (2H, m, lactam CH ×2), 1.90-1.76 (2H, m, lactam CH x2), 1.55- 1.21 (18H, m, lactam CH ×2+ chain (CH2)3), 1.16 (3H, d, J 7, CHCH3) and 0.88 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 175.9, 175.7 (CO), 72.0 (CHOH), 52.1 (NCH), 44.8 (CHCH3), 42.1 (NCH2), 33.7, 31.9, 31.4, 29.6 (×2), 29.5, 29.3, 28.8, 27.9, 26.0, 22.7 (CH2), 14.1 and 10.7 (CH3); m/z (MH+ C19H37N2O3 requires 341.2804) 341.2803.

38. Single Step



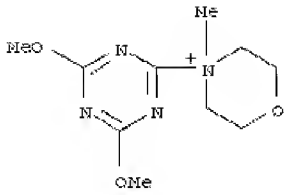
• HCl

72%

Overview

Steps/Stages **Notes**

1.1 R:



S:MeOH, rt → 0°C; 4 h, 0°C

1) reaction from p.45 in patent, Reactants: 2, Reagents: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

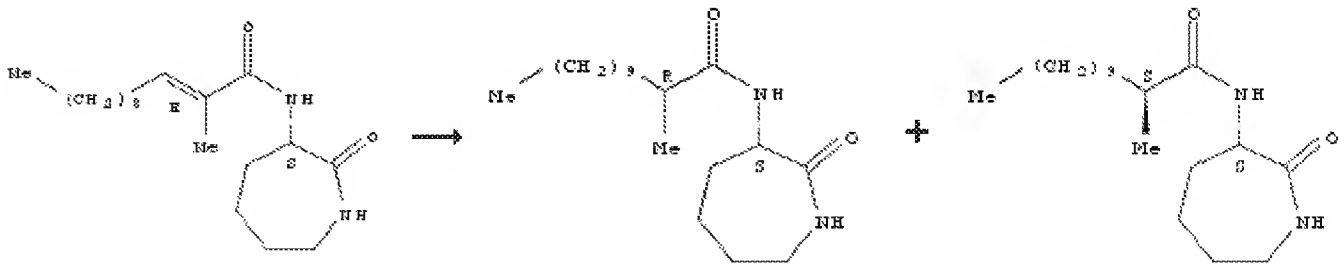
From PCT Int. Appl., 2005053702, 16 Jun 2005

R:Et_3N,

Experimental Procedure

Example 55: (3S,2'S,3'R)-3-(3-Hydroxy-2'-methyldecanoyl)amino-caprolactam: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (1.40 mmol) was dissolved in MeOH (10 ml), and (S)-3-amino-caprolactam hydrochloride (1.50 mmol) and triethylamine (2 mmol) were added. The reaction was cooled to 0 °C and 4-(4,6-dimethoxy[1,3,5]triazin- 2-yl)-4-methyl-morpholinium chloride (1.40 mmol) was added. The reaction was stirred for 4 hours, and then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with dilute aqueous HCl and dilute aqueous NaOH, and then dried over Na2SO4. The solvent was removed in vacuo and the residue was recrystallised form ethyl acetate / hexane to give (3S,2'S,3'R)-3-(3'-hydroxy-2'-methyldecanoyl)amino-caprolactam as a solid (341 mg, 72%) (3S,2'S,3'R)-3-(3-Hydroxy-2'-methyldecanoyl)amino-caprolactam, Yield (341 mg, 72%). m.p.(hexanes) 88-91 °C; vmax/cm-1 3313 (NH), 1628 (CO), 1480 (NH); [α]25D (c = 0.5, CHCl3) +40.8; δH (500 MHz, CDCl3) 7.08 (1H, d J 5.5, NHCH), 6.51 (1H, br 8, NHCH2), 4.57 (1H, ddd, J 11, 6.5, 1, NCH), 3.83 (1H, dt, J8, 4, CHOH), 3.36-3.21 (2H, m, NCH2), 2.40 (1H, dq, J7, 3, CHCH3), 2.12-1.96 (2H, m, lactam CH ×2), 1.90- 1.76 (2H, m, lactam CH x2), 1.55-1.34 (4H, m, lactam CH ×2 + chain CH2), 1.34-1.21 (14H, m, (CH2),), 1.17 (3H, d, J 7, CHCH3) and 0.88 (3H, t, J7, CH2CH,) (OH not observed); δc (125 MHz, CDCl3) 175.8, 175.7 (CO), 72.1 (CHOH), 52.0 (NCH), 44.6 (CHCH3), 42.1 (NCH2), 33.4, 31.9, 31.3, 29.6 (x2), 29.5, 29.3, 28.8, 27.9, 26.1, 22.7 (CH2), 14.1 and 11.2 (CH3); m/z (MH+ C19H37N2O3 requires 341.2804) 341.2776.

39. Single Step



Overview

Steps/Stages **Notes**

1.1 R:H_2, C:$Pd(OH)_2$, S:MeOH, 18 h, rt

1) stereoselective, overall yield is greater than 95%, reaction from p.43 in patent, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

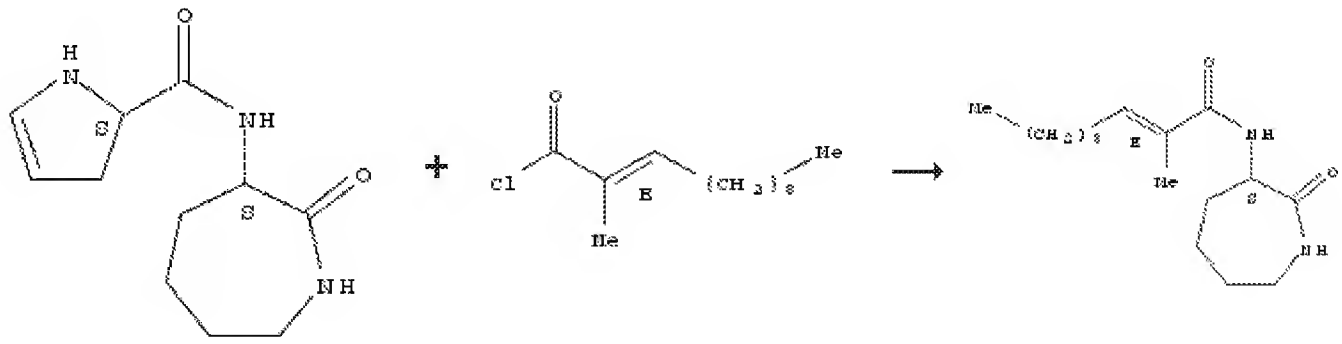
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2,-Methyldodecanoyl)amino-caprolactam: (5)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam (0.5 mmol) and Pd(OH)2 (20% on carbon) were added to methanol (10 ml) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of hydrogen. The reaction was then filtered, and the solvent removed in vacuo to give (3S,2R) and (3S',2'S)-3-(2'-methyldodecanoyl)amino-caprolactam as a solid (160 mg, >95%). Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2,-Methyldodecanoyl)amino-caprolactam, Yield (160 mg, >95%). νmax/cm-1 3313 (NH), 1671, 1636 (CO), 1515 (NH); δH (500 MHz, CDCl3) 6.91 (2H, d, J 5.5, CHNH, both isomers), 6.55 (2H, br s, CH2NH, both isomers), 4.57-4.47 (2H, m, CHNH, both isomers), 3.34-3.18 (4H, m, CH2NH, both isomers), 2.29-2.14 (2H, CH3CHCO, both isomers), 2.07 (2H, br d, J13.5, lactam ring CH, both isomers), 2.02-1.94 (2H, m, lactam ring CH, both isomers), 1.89-1.76 (4H, m, lactam ring CH x2, both isomers), 1.67-1.57 (2H, m, chain CH, both isomers), 1.51-1.33 (6H, m, lactam ring CH ×2 + side chain CH2, both isomers), 1.32-1.18 (32H, m, (CH2)8, both isomers), 1.13 (3H, d, J 7, CHCH3, one isomer), 1.11 (3H, d, J7, CHCH,, one isomer) and 0.87 (6H, t, J7.5, CH3, both isomers); δc (125 MHz, CDCl3) 175.9 (×2), 175.8 (×2)(CO, both isomers), 52.0, 51.9 (NCH), 42.1 (x2) (NCH2, both isomers), 41.3, 41.2 (CHCH3), 34.5, 34.1, 31.9 (x2), 31.8, 31.7, 29.6 (×6), 29.5 (×2), 29.3 (×2), 28.9 (×2), 28.0, 27.9, 27.4 (×2), 22.6 (×2) (CH2) 17.8, 17.6 and 14.1 (×2) (CH3); m/z (MH+ C19H37N2O2 requires 325.2855) 325.2858.

40. Single Step



65%

Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

1) reaction from p.42 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

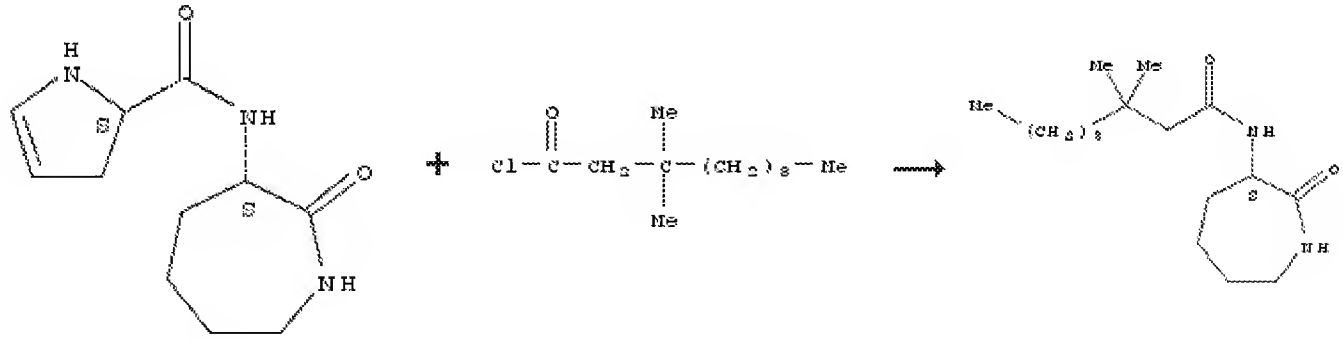
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 49: (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na2CO3 (6 mmol) in water (15 ml) were added to a solution of (E)-2-methyldodec-2-enoyl chloride (1.43 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was recrystallised from hexane to give (5)-(E)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam (297 mg, 65%). (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam, Yield (297 mg, 65%). m.p. (hexanes) 99-100 °C; vmax/cm-1 3282 (NH), 1656,1622 (CO and C=C), 1497 (NH); [α]25D (c = 1, CHCl3) +38.2; 5H (500 MHz, CDCl3) 7.15 (1H, d, J5.5, NHCH), 6.48-6.35 (2H, m, NHCH2 + CH=C), 4.54 (1H, ddd, J11, 5.5, 1.5, NHCH), 3.33-3.17 (2H, m, CHNH), 2.14-2.05 (3H, m, CH2CH=C + lactam ring CH), 2.02-1.93 (1H, m, lactam ring CH), 1.88-1.77 (5H,m, lactam ring CH x2 + CH3C=CH), 1.47-1.31 (4H, brm, lactam ring CH x2 + chain CH2), 1.31-1.17 (12H, m, (CH2)6) and 0.85 (3H, t, J7, CH2CH3); δC (125 MHz, CDCl3) 175.9,168.2 (CO), 136.9 (CH=C), 130.2 (CH=C, 52.3 (NHCH), 42.2 (NHCH2), 31.8, 31.6, 29.5, 29.4 (x2), 29.3, 28.9,28.7, 28.3, 27.9, 22.6 (CH2), 14.1 and 12.4 (CH3).

41. Single Step



68%

Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

1) reaction from p.41 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

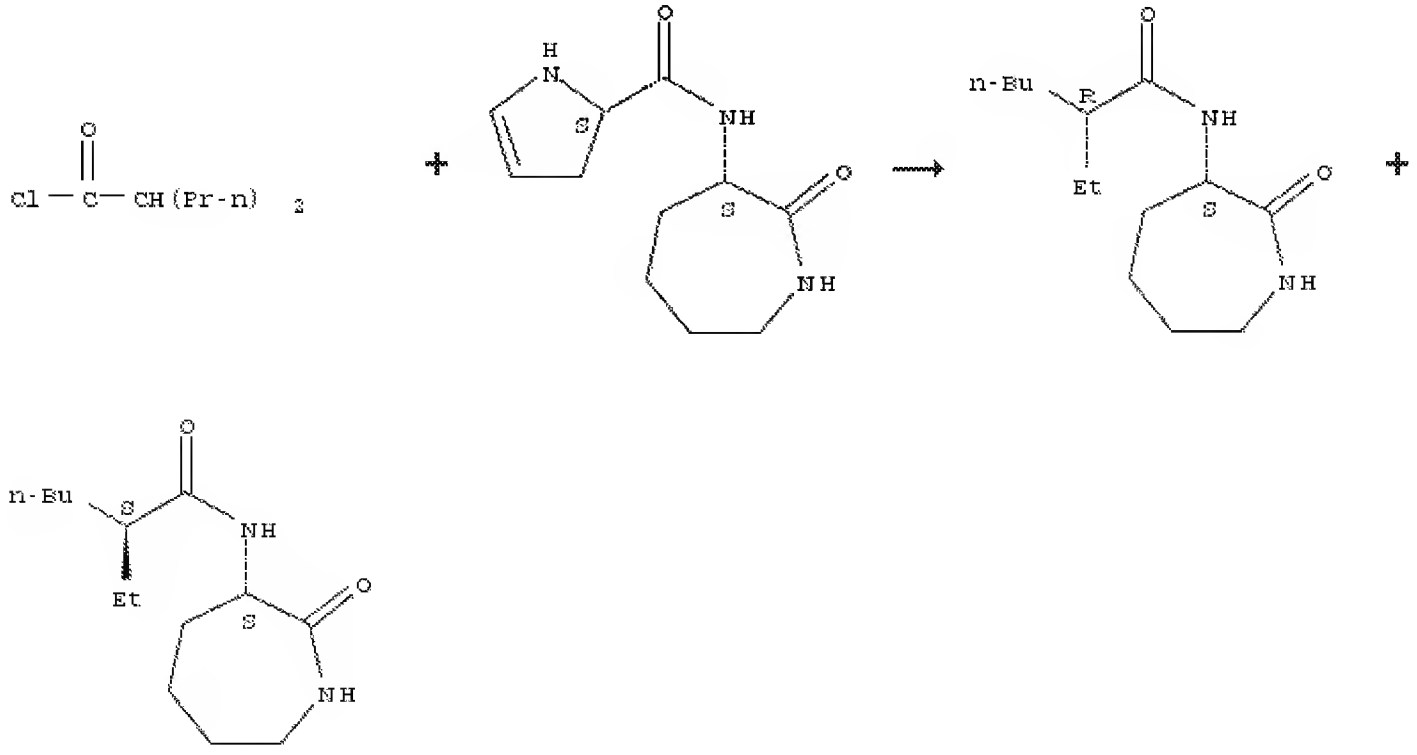
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 45: (S)-3-(3',3'-Dimethyldodecanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of 3,3-dimethyldodecanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacua. The residue was recrystallised from hexane to give (5)-3-(3',3'-dimethyldodecanoyl)amino-caprolactam (1.14 g, 68%) (S)-3-(3',3'-Dimethyldodecanoyl)amino-caprolactam, Yield (1.14 g, 68%). m.p. (hexanes) 123-125 °C; [α] 25D (c = 1, CHCl3) +28.6; νmax/cm-1 3279 (NH), 1646 (CO), 1498 (NH); δH (500 MHz, CDCl3) 6.81 (1H, d, J 5.5, CHNR), 6.59-6.42 (1H, br m, CH2NH), 4.50 (1H, ddd, J11, 6, 1.5, CHNH), 3.30-3.16 (2H, m, CH2NH), 2.08-2.02 (3H, m, CH2CO + lactam ring CH), 2.00-1.90 (1H, m, lactam ring CH), 1.86-1.75 (2H, m, lactam ring CH x2), 1.47-1.31 (2H, br m, lactam ring CH x2), 1.30-1.17 (16H, m, (CH2)8), 0.89 (6H, s, C(CH3)2) and 0.84 (3H, t, J 7, CH2SO2); δc (125 MHz, CDCl3) 175.8, 170.9 (CO), 52.0 (NHCH), 48.4, 42.6, 41.1 (CH2), 33.3 (CMe2), 31.9, 31.7, 30.4, 29.7, 29.6, 29.3, 28.9, 27.9 (CH2), 27.3 (x2) (CH3), 24.1, 22.6 (CH2) and 14.1 (CH3); m/z (M+ C20H38N2O2 requires 338.2933) 338.2928.

42. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) combined yield = 26%, reaction from p.39 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

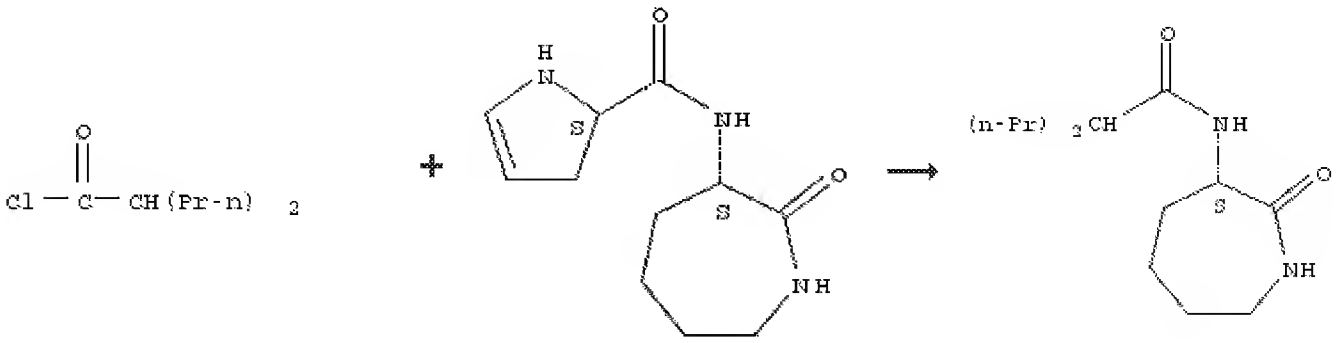
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 42(a): (3S,2'R) and Example 42(b): (3S',2'R)-3-(2'-Ethylhexanoyl)amino-caprolactam: (S,S)-S-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of (+/-) 2-ethylhexanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacuo. The residue was recrystallised from hexane to give a mixture of (ZS,2'R) and (3S,2'S)-3-(2'-ethylhexanoyl)amino-caprolactam (328 mg, 26%). Example 42(a): (3S,2'R) and Example 42(b): (3S',2'R)-3-(2'-Ethylhexanoyl)amino-caprolactam, Yield (328 mg, 26%). νmax/cm-1 3306 (NH), 1686, 1633 (CO), 1537 (NH); δH (500 MHz, CDCl3) 6.89 (2H, d, J 5, CHNH, both isomers), 6.53 (2H, br s, CH2NH, both isomers), 4.52 (2H, ddd, J11, 6, 1.5, CHNH, both isomers), 3.30-3.16 (4H, m, CH2NH, both isomers), 2.06 (2H, br d, J13.5, lactam CH ×2, both isomers), 2.02-1.92 (4H, m, (CH2)2CHCO ×2 and lactam ring CH ×2, both isomers), 1.86-1.74 (4H, m, lactam ring CH ×4, both isomers), 1.63-1.50 (4H, m, sidechain CH2), 1.50-1.30 (8H, m, lactam ring CH ×4+ sidechain CH2 ×4, both isomers), 1.30-1.14 (8H, m, side chain CH2 x8, both isomers), 0.85 (3H, t, J 7.5, CH3, one isomer) and 0.82 (3H, t, J7.5, CH3, one isomer); δc (125 MHz, CDCl3) 175.8, 175.1 (CO), 52.0, 51.9 (NHCHCO), 49.3 (x2) (CH), 42.0 (×2), 32.5, 32.3, 31.7 (×2), 29.7 (x2), 28.8 (×2), 27.9 (×2), 26.1, 25.9, 22.7 (x2), 14.0, 13.9 (CH3) and 12.0 (×2)(CH3); m/z (M+ C14H26N2O2 requires 254.1994) 254.1995.

43. Single Step



80%

Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

1) reaction from p.39 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

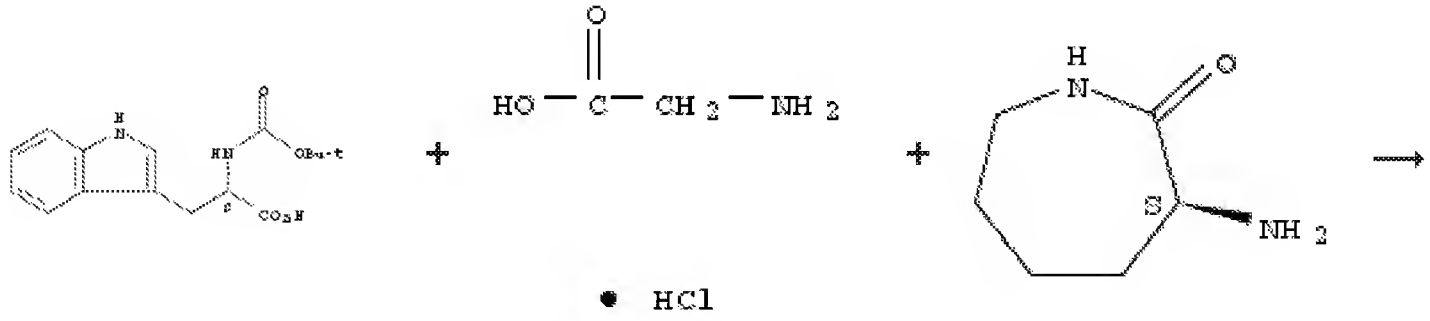
By Grainger, David John, Fox, David John

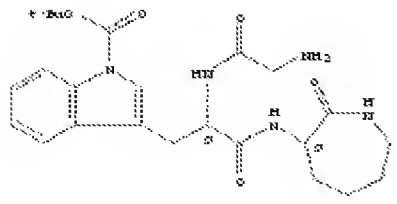
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 41: (S)-3-(2'-Propylpentanoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-3-carboxylate (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of 2-propylpentanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacuo. The residue was recrystallised from hexane to give (S)-3-(2'-propylpentanoyl)amino-caprolactam (1.02 g, 80%). (S)-3-(2'-Propylpentanoyl)amino-caprolactam, Yield (1.02 g, 80%). m.p. (hexanes) 114-118 °C; [α]25D (c = 1, CHCl3) +29.4; νmax/cm-1 3303 (NH), 1686, 1633 (CO), 1537 (NH); δH (500 MHz, CDCl3) 6.88 (1H, d, J 5.5, CHNH), 6.52 (1H, br s, CH2NH), 4.52 (1H, ddd, J11, 6, 1.5, CHNH), 3.30-3.16 (2H, m, CH2NH), 2.13-2.02 (2H, m, (CH2)2CHCO and lactam ring CH), 2.02-1.92 (1H, m, lactam ring CH), 1.86-1.74 (2H, m, lactam ring CH x2), 1.57-1.50 (2H, m, sidechain CH2), 1.42 (1H, br qd, J13.5, 3.5, lactam ring CH), 1.38-1.29 (2H, m, lactam ring CH + side chain CH2), 1.29-1.19 (4H, m, sidechain CH ×4), 0.85 (3H, t, J7.5, CH3) and 0.84 (3H, t, J 7.5, CH3); δc (125 MHz, CDCl3) 175.8, 175.2 (CO), 51.9 (NHCHCO), 47.2 (CH), 42.1, 35.3, 35.1, 31.7, 28.9, 27.9, 20.7 (×2) (CH,) and 14.1 (x2)(CH,); m/z (MH+ C14H27N2O2 requires 255.2073) 255.2083.

44. Single Step





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Overview

Steps/Stages **Notes**

1) solid-supported reaction, solid-phase automated peptide synthesizer used, reaction from p.35 in patent, Reactants: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

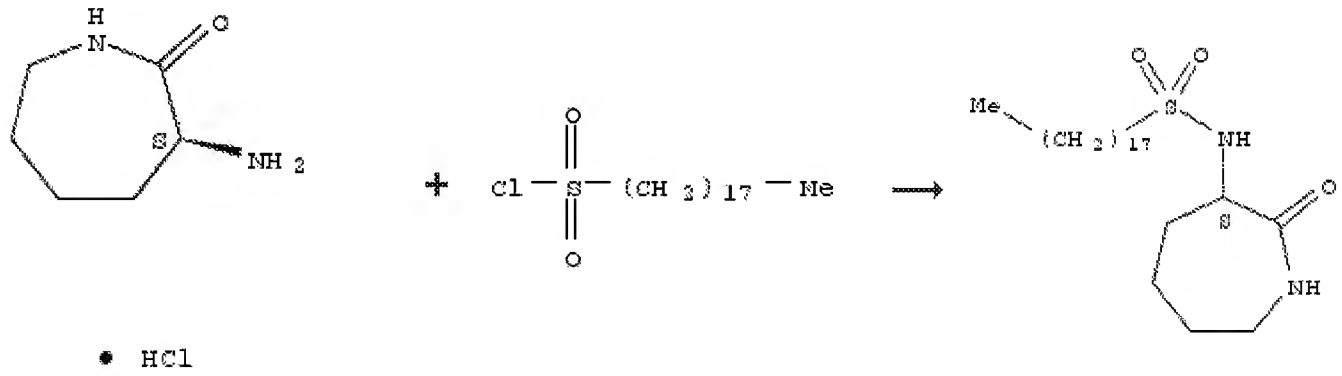
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 33: (S)-aminocaprolactam-Glycine-(L)-N(Boc)-Tryptophan: This tripeptide was made on a solid-phase automated peptide synthesiser using (S)- aminocaprolactam for the final peptide coupling step. Mr(Calc) = 471.5110. Observed Mr by mass spectrometry 471.6. Purity (%TIC in molecular ion peak) = 90% (S)-aminocaprolactam-Glycine-(L)-N(Boc)-Tryptophan, Yield 471.6. 90%.

45. Single Step



61%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 10 h, rt

Notes

1) reaction from p.35 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

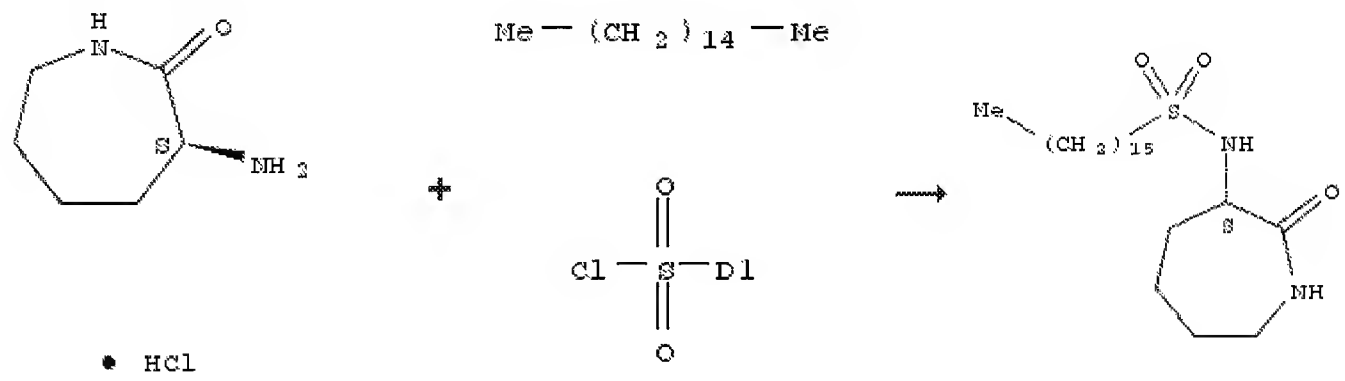
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 32: (S)-3-(Octadecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (20 ml) were added to a solution of octadecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(octadecanesulfonyl)amino-caprolactam (545 mg, 61%). (S)-3-(Octadecanesulfonyl)amino-caprolactam, Yield (545 mg, 61%). m.p. 99-100 °C; νmax/cm-1 3356, 3249 (NH), 1659 (CO), 1323, 1140 (SO2N); δH (500 MHz, CDCl3) 6.15 (1H, t, J 6, CH2NH), 5.69 (1H, d, J 6, CHNH), 4.12 (1H, ddd, J11.5, 6, 2, CHNH), 3.30-3.18 (2H, m, CH2NH), 2.97-2.92 (2H, m, CH2SO2), 2.12-2.07 (1H, m, ring CH), 2.06-1.97 (1H, m, ring CH), 1.87-1.56 (5H, m, CH2CH2SO2+ 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH2), 1.32-1.18 (28H, m, chain CH2) and 0.86 (3H, m, CH3); m/z (MNa+ C24H48N2O3SNa requires 467.3277852) 467.330047.

46. Single Step



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Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 10 h, rt

Notes

1) reaction from p.34 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

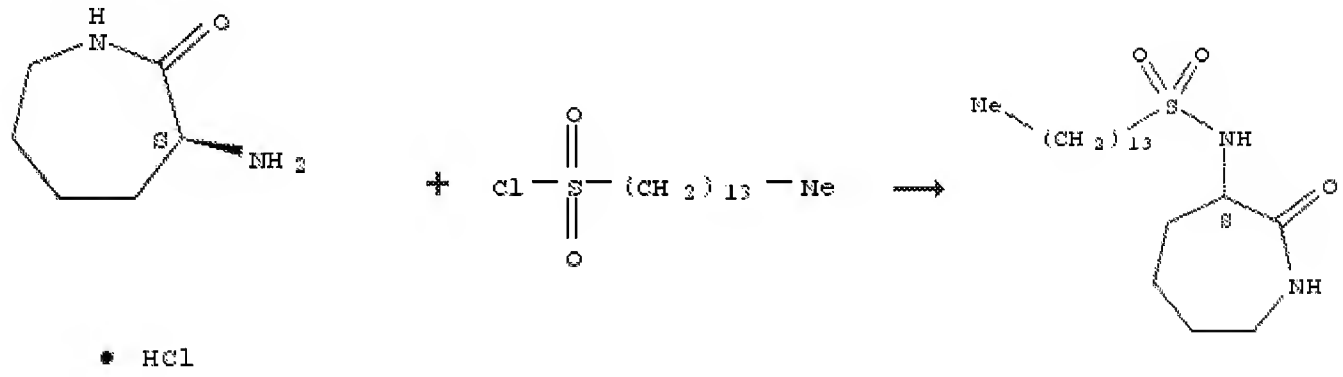
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 31; (S)-3-(Hexadecanesulfonyl)amino-caprolactam: (6)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (20 ml) were added to a solution of hexadecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over 1N Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(hexadecanesulfonyl)amino-caprolactain (553 mg, 66%). (S)-3-(hexadecanesulfonyl)amino-caprolactain, Yield (553 mg, 66%). m.p. 100-101 °C; [α]25D (c = 1, CHCl3) +14.1; νmax/cm-1 3356, 3249 (NH), 1659 (CO), 1323, 1140 (SO2N); δH (500 MHz, CDCl3) 6.55 (1H, t, J6, CH2NH), 5.76 (1H, d, J 6, CHNH), 4.1·1 (1H, ddd, J 11.5, 6, 2, CHNH), 3.30-3.17 (2H, m, CH2NH), 2.94 (2H, t, J8, CH2SO2), 2.12-2.04 (1H, m, ring CH), 2.04-1.97 (1H, m, ring CH), 1.87-1.58 (5H, m, CH2CH2SO2+ 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH2), 1.32-1.18 (24H, m, chain CH2) and 0.86 (3H, m, CH3); δc (125 MHz, CDCl3) 174.9 (CO) 55.5 (NHCHCO), 53.5 (CH2SO2), 42.1 (NCH2), 33.8, 31.9, 29.7 (×2), 29.6 (×4), 29.5, 29.3 (×2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH2), and 14.1 (CH3); m/z (MNa+ C20H40N2O3SNa requires 439.2965) 439.2980; anal (C22H44N2O3S requires C, 63.4, H, 10.6, N, 6.7) C, 63.1, H, 10.6, N, 6.6.

47. Single Step



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Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 10 h, rt

Notes

1) reaction from p.34 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

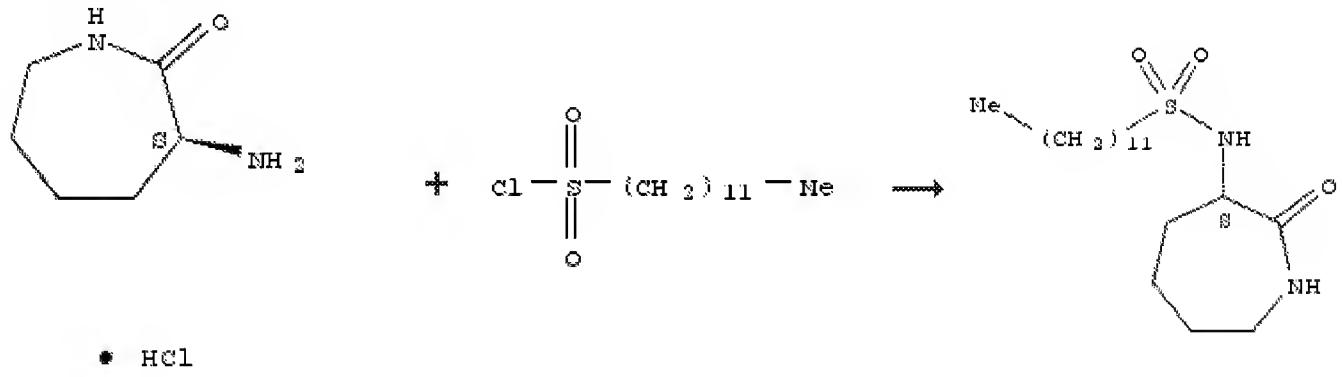
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 30: (S)-3-(Tetradecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (20 ml) were added to a solution of tetradecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1to 100% EtOAc) and then by recrystallisation from heptane to give (5)-3-(tetradecanesulfonyl)amino-caprolactam (373 mg, 48%). (S)-3-(Tetradecanesulfonyl)amino-caprolactam, Yield (373 mg, 48%). m.p. 100-101 °C; [α]25D (c = 1, CHCl3)+14.4; νmax/cm-1 3361, 3250 (NH), 1658 (CO), 1324, 1140 (SO2N); δH (500 MHz, CDCl3) 6.64 (1H, t, J6, CH2NH), 5.74 (1H, d, J6, CHNH), 4.11 (1H, ddd, J11.5, 6, 2, CHNH), 3.30-3.17 (2H, m, CH2NH), 2.97-2.92 (2H, m, CH2SO2), 2.12-2.05 (1H, m, ring CH), 2.05-1.96 (1H, m, ring CH), 1.87-1.59 (5H, m, CH2CH2SO2+ 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH2), 1.32-1.18 (20H, m, chain CH2) and 0.86 (3H, m, CH3); δc (125 MHz, CDCl3) 174.9 (CO) 55.5 (NHCHCO), 53.4 (CH2SO2), 42.2 (NCH2), 33.8, 31.9, 29.6 (×4), 29.5, 29.3 (x2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH2), and 14.1 (CH3); m/z (MNa+ C20H40N2O3SNa requires 411.2652) 411.2655; anal (C20H40N2O3S requires C, 61.8, H, 10.4, N, 7.2) C, 61.9, H, 10.5, N, 7.2.

48. Single Step



42%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 10 h, rt

Notes

1) reaction from p.33 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

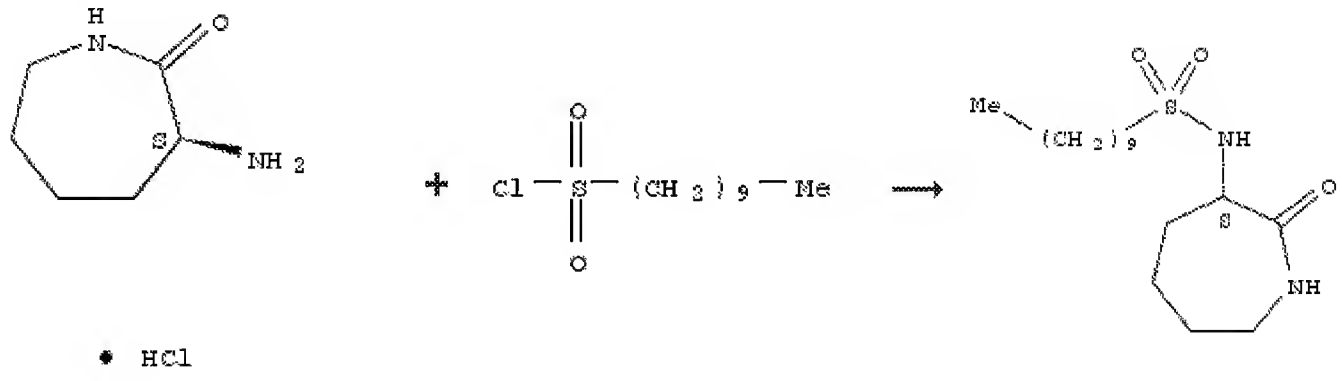
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 29: (S)-3-(Dodecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (20 ml) were added to a solution of dodecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:lto 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(dodecanesulfonyl)amino-caprolactam (302 mg, 42%). (S)-3-(Dodecanesulfonyl)amino-caprolactam, Yield (302 mg, 42%). m.p. 100-101 °C; [α]25D (c = 1, MeOH)+22.4; νmax/cm-1 3366, 3247 (NH), 1657 (CO), 1324, 1143 (SO2N); δH (500 MHz, CDCl3) 6.66 (1H, t, J6, CH2NH), 5.78 (1H, d, J6, CHNH), 4.10 (1H, ddd, J11, 6, 2, CHNH), 3.29-3.17 (2H, m, CH2NH), 2.97-2.90 (2H, m, CH2SO2), 2.12-2.03 (1H, m, ring CH), 2.03-1.96 (1H, m, ring CH), 1.88-1.59 (5H, m, CH2CH2SO2+ 3 ring CH), 1.43-1.32 (3H, m, ring CH + chain CH2), 1.32-1.18 (16H, m) and 0.85 (3H, m, CH3); δc (125 MHz, CDCl3) 175.0 (CO) 55.5 (NHCHCO), 53.5 (CH2SO2), 42.1 (NCH2), 33.8, 31.8, 29.6 (x2), 29.5, 29.3 (×2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH2), and 14.1 (CH3); m/z (MNa+ C18H36N2O3SNa requires 383.2339) 383.2351; ana1 (C18H36N2O3S requires C, 60.0, H, 10.1, N, 7.8) C, 59.9, H, 10.2, N, 7.7.

49. Single Step



48%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 10 h, rt

Notes

1) reaction from p.33 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

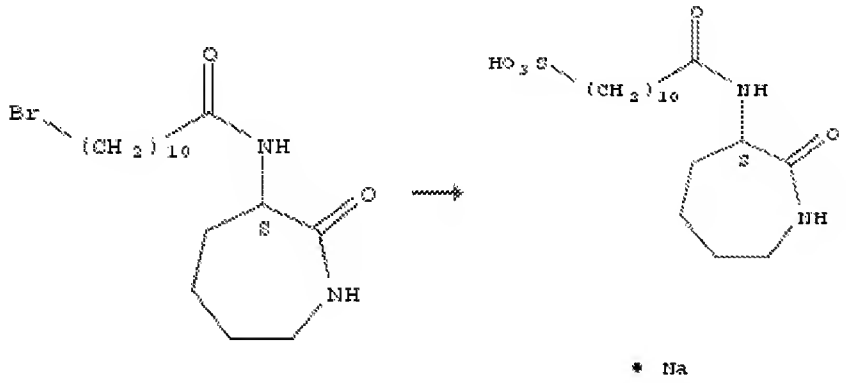
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 28: (S)-3-(Decanesulfonyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (3 mmol) and Na2CO3 (9 mmol) in water (20 ml) were added to a solution of decanesulfonylchloride (3 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc / hexanes to give (5)-3-(decanesulfonyl)amino-caprolactam (481 mg, 48%). (S)-3-(Decanesulfonyl)amino-caprolactam, Yield (481 mg, 48%). m.p. 98-99 °C; [α]25D (c = 1, MeOH) +22.7; νmax/cm-1 3365, 3248 (NH), 1657 (CO), 1324, 1142 (SO2N); δH (500 MHz, CDCl3) 6.35-6.18 (1H, m, CH2NH), 5.71 (1H, d, J 6, CHNH), 4.11 (1H, ddd, J11.5, 6, 2, CHNH), 3.31-3.18 (2H, m, CH2NH), 2.98-2.92 (2H, m, CH2SO2), 2.09 (1H, br d, J 14, ring CH), 2.06-1.97 (1H, m, ring CH), 1.88-1.59 (5H, m, CH2CH2SO2+ 3 ring CH), 1.43-1.33 (3H, m, chain CH2 + ring CH), 1.32-1.18 (12H, m, CH3(CH2)6) and 0.86 (3H, m, CH3); δc (125 MHz, CDCl3) 174.8 (CO) 55.5 (NHCHCO), 53.5 (CH2SO2), 40.7 (NCH2), 33.9, 31.8, 29.4, 29.3, 29.2, 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH2), and 14.1 (CH3); m/z (MNa+ C15H32N2O3SNa requires 355.2031) 355.2054; anal (C16H32N2O3S requires C, 57.8, H, 9.7, N, 8.4) C, 57.8, H, 9.7, N, 8.3.

50. Single Step



97%

Overview

Steps/Stages

1.1 R:Na_2SO_3, S:H_2O, S:EtOH, 14 h, reflux; cooled

Notes

1) reaction from p.32 in patent, Reactants: 1, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

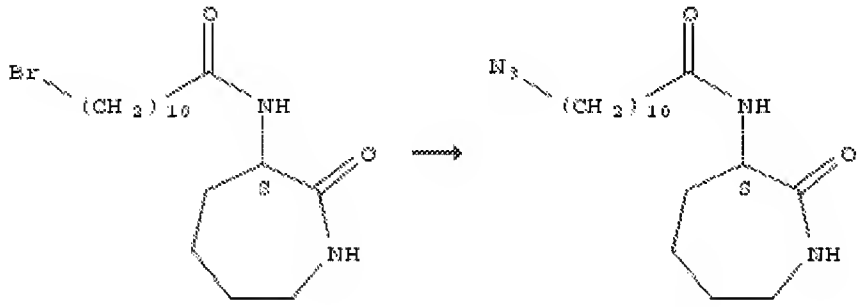
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 27: (5) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate: sodium sulfite (630 mg, 5 mmol) in water (3 ml) was added to (1S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in ethanol (2 ml) and the mixture was heated at reflux for 14 hours. The cooled reaction mixture was then added to ethanol (25 ml) and the reaction was filtered. The solvent was then removed in vacuo to give (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate (456 mg, 97%) (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate, Yield (456 mg, 97%). m.p. (EtOAc) 208-210 °C; [α]D25 (c = 1, H2O) -15.5; νmax/cm-1 3430, 3344, 3289 (NH + H2O), 1667, 1643 (CO), 1530 (NH) 1195, 1183 (SO3, asymm.), 1064 (SO3, symm.); δH (500 MHz, d6-DMSO) 7.76 (1H, t, J 6, CH2NH), 7.70 (1H, d, J7, CHNH), 4.35 (1H, dd, J10, 7.5, CHNH), 3.42 (8H, s, 4 × H2O) 3.17-3.00 (2H, m, CH2NH), 2.47-2.38 (2H, m, CH2SO3), 2.17-2.05 (2H, m, CH2CONH), 1.82 (1H, br s, J13.5, C-5 H), 1.75-1.66 (2H, m, C-4 H, C-6 H), 1.65- 1.50 (3H, m, C-5 H + chain CH2), 1.47-1.40 (2H, m, chain CH2) 1.35 (1H, qd, J13, 3, C-4 H), and 1.30-1.11 (13H, m, (CH2), + C-6 H); Sc (125 MHz, d6-DMSO) 174.5 (CO-ring), 171.5 (CO-chain), 51.6 (CH2SO3), 51.4 (NHCHCO), 40.8 (NCH2), 35.3, 31.3, 29.1 (×3), 29.0 (x2), 28.8, 28.6, 27.8, 25.5 and 25.1 (CH2); m/z MNa+ C17H31N2O5SNa2 requires 421.1749) 421.1748.

51. Single Step



66%

Overview

Steps/Stages

1.1 R:NaN_3, S:DMF, 14 h, 60°C

Notes

1) reaction from p.31 in patent, Reactants: 1, Reagents: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

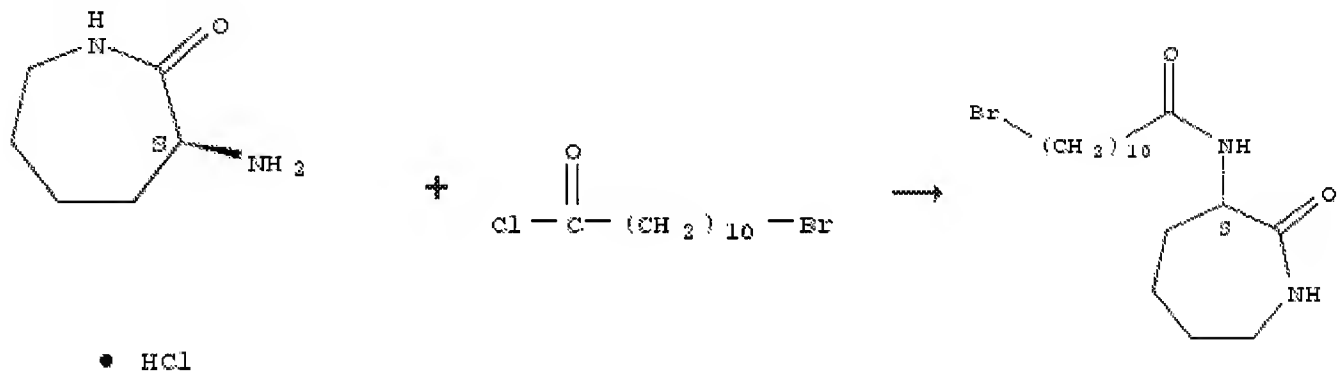
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 26: (S)-3-(11'-azido-undecanoyl)amino-caprolactam: Sodium azide (650 mg, 10 mmol) was added to (S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in DMF (2 ml) and the mixture was heated at 60 °C for 14 hours. The solvent was then removed in vacuo and the residue was partitioned between water (20 ml) and EtOAc (3 x 20 ml). The combined organic layers were washed with 1M HCl aq (2 x 20 ml) and then dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (5)-3-(11'-azido-undecanoyl)amino-caprolactam (221 mg, 66%). (S)-3-(11'-azido-undecanoyl)amino-caprolactam, Yield (221 mg, 66%). m.p. (EtOAc) 71-72 °C; [α]25D (c= 1, CHCl3) +34.7; νmax/cm-1 3344, 3289 (NH), 2101 (N3) 1668, 1631 (CO), 1516 (NH); δH (500 MHz, d6-DMSO) 7.77 (1H, t, J 6, CH2NH), 7.67 (1H, d, J7, CHNH), 4.38 (1H, dd, J l1, 7, CHNH), 3.30 (2H, t, J 7, CH2N3), 3.15 (1H, ddd, J15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 5.5, CHHNH), 2.17-2.07 (2H, m, CH2CONH), 1.85 (1H, dt, J14, 3.5, C-5 H), 1.82-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, qt, J 13, 3.5, C-5 H), 1.51 (4H, m, CH2CH2CONH and CH2CH2N3), 1.36 (1H, qd, J13, 3, C-4 H), and 1.33-1.13 (13H, m, (CH2)6 + C-6 H); δc (125 MHz, d6-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 50.7 (CH2N3), 40.7 (NCH2), 35.3, 31.3, 29.0 (×2), 28.9, 28.7, 28.6, 28.3, 27.8, 26.2 and 25.4 (CH2); m/z (MNa+ C17H31N2O2Na requires 360.2375) 360.2360.

52. Single Step



79%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 4 h, rt

Notes

1) reaction from p.31 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

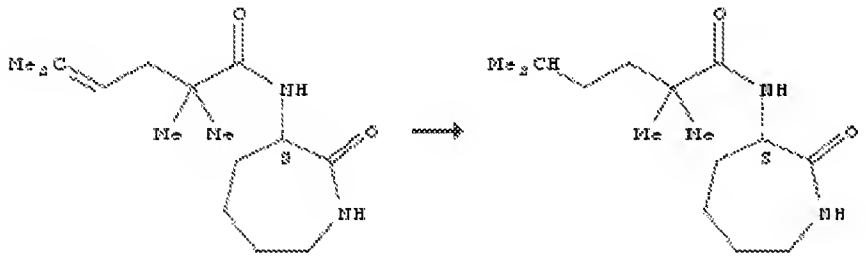
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na2CO3 (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]25D (c = 1, CHCl3) +31.8; νmax/cm-1 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δH (500 MHz, d6-DMSO) 7.76 (1H, t, J6.5, CH2NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J11, 7, CHNH), 3.51 (2H, t, J6.5, CH2Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 7, CHHNH), 2.17-2.06 (2H, m, CH2CONH), 1.85 (1H, dt, J14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH2CH2Br), 1.62 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br qn J6.5, CH2CH2CONH), 1.41-1.31 (3H, m, C-4 H and chain CH2) and 1.31-1.13 (11H, m, (CH2)8 + C-6 H); δc (125 MHz, d6-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH2), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH2); m/z (MH+ BrC17H32N2O2 requires 375.1647) 375.1655.

53. Single Step



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Overview

Steps/Stages

1.1 R:H_2, C:$Pd(OH)_2$, S:AcOEt, 14 h, rt

Notes

1) reaction from p.30 in patent, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

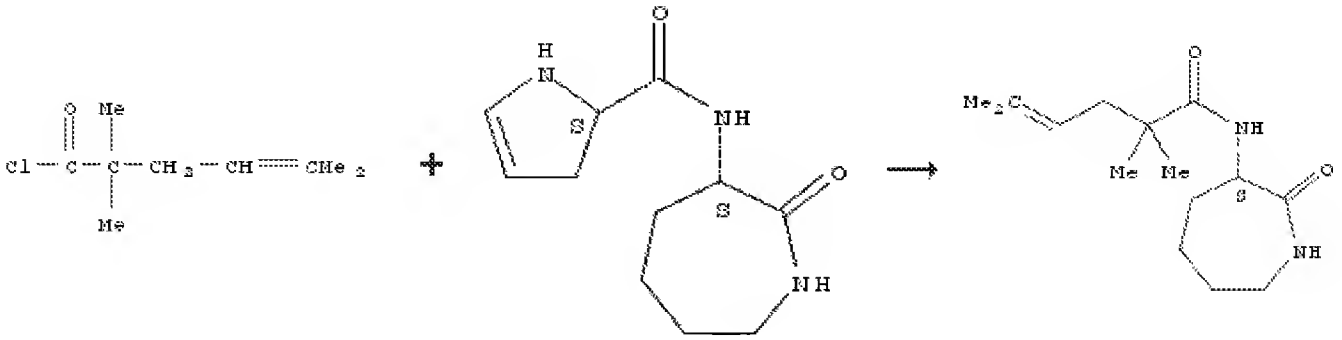
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 24: (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmostsphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (6)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]25D (c=1, CHCl3) +27.8; νmax/cm-1 3249 (NH), 1654, 1638 (CO), 1502 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5.0, CHNH), 6.75-6.55 (1H, br m, CH2NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH2 + CH(CH3)2), 1.13 (3H, s, CH3), 1.12 (3H, 8, CH3), 1.08-1.02 (2H, m, CH2), 0.82 (3H, s, CH3), 0.80 (3H, s, CH3); δc (125 MHz, CDCl3) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH2N), 41.9 (CH2CMe2), 39.0, 33.7, 31.5, 28.9 (CH2), 28.4 (Me2CH), 27.9 (CH2), 25.3, 25.2, 22.6, 22.5 (CH3); m/z (MH+ C15H29N2O2 requires 269.2229) 269.2219.

54. Single Step



84%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.30 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

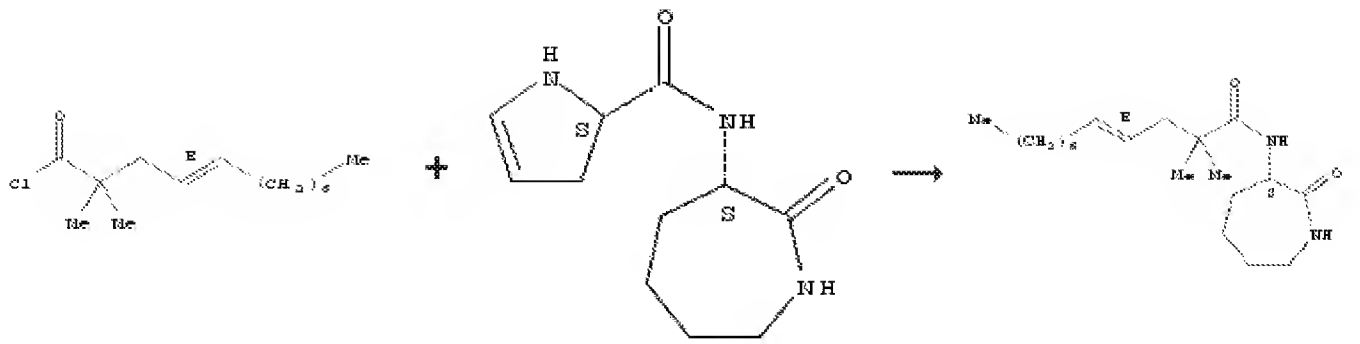
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na2CO3 (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]25D (c = 1, CHCl3) +23.2; vmax/cm-1 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δH (500 MHz, CDCl3) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH2NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH2NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH2), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH2), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH3), 1.56 (3H, s, CH3), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH3) and 1.12 (3H, s, CH3); δc (125 MHz, CDCl3) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH2CMe2), 42.1 (CH2N), 39.0, 31.5, 28.9, 28.0 (CH2 lactam), 26.0, 25.0, 24.9, 17.9 (CH3); m/z (MH+ C15H27N2O2 requires 267.2073)267.2063.

55. Single Step



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Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.29 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

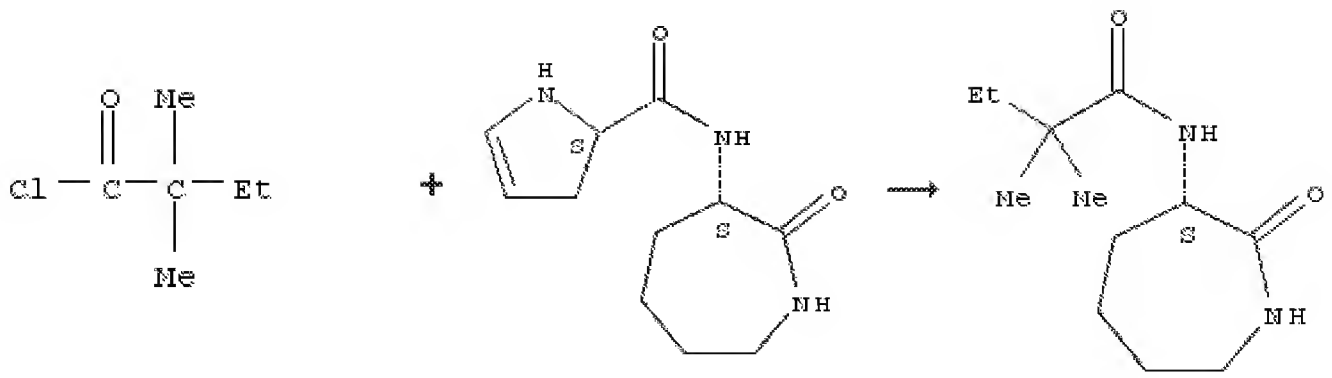
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na2CO3 (3 0 mmol) in water (3 0 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). [α]25D (c = 1, CHCl3 +21.6; νmax/cm-1 3264 (NH), 1639 (CO), 1497 (NH); δH (500 MHz, CDCl3) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH2NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30- 3.17 (2H, m, CH2NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH2), 2.14 (1H, dd, 13.5, 7, CH=CHCH2), 2.01-1.87 (4H, br m, ring CH x2, + CH2CH=CH), 1.87-1.'74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH2)3) 1.1 3 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH2), 42.1 (x2)(CH2+ CMe2), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH2), 25.0, 24.8 (CH3) and 22.6 (CH3); m/z (MH+ C20H37N2O2 requires 337.2855) 337.2858.

56. Single Step



50%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.29 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

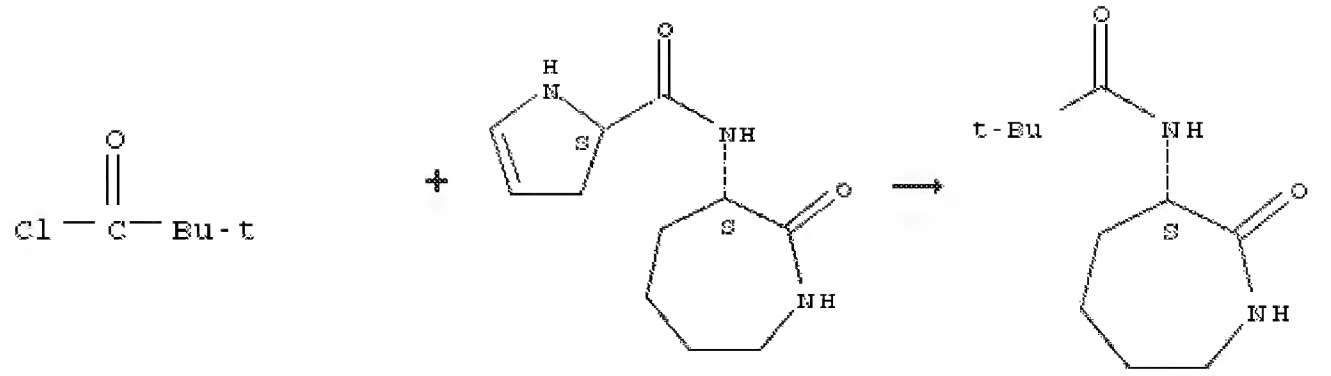
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 21: (S)-3-(2',2'-Dimethyl-butyryl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-S-carboxylate (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-butyryl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacuo. The residue was recrystallised from EtOAc / hexane to give (5)-3-(2',2'-dimethylpropionyl) amino-caprolactam (562 mg, 50%) (S)-3-(2',2'-Dimethyl-butyryl)amino-caprolactam, Yield (562 mg, 50%). m.p. 106-107 °C; [α]25D (c = 1, CHCl3)+33.6; νmax/cm-1 3400, 3278 (NH), 1677, 1630 (CO), 1500 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5.0, CHNH), 6.72 (1H, br s, CH2NH), 4.44(1H, ddd, J 11, 5.5, 1.5, CRNH), 3.28-3.16 (2H, m, CH2NH), 2.04-1.90 (2H, m, 2 × ring CH), 1.83-1.72 (2H, m, 2 × ring CH), 1.57-1.44 (2H, m, CH2CH3), 1.44-1.30 (2H, m, 2 × ring CH) 1.12 (3H, s, CH3) 1.11 (3H, s, CH3) and 0.78 (3H, t, J 7.5, CH2CH3); δc (125 MHz, CDCl3) 177.0, 176.0 (CO), 52.1 (NHCHCO), 42.2 (CCO), 42.0 (CH2N), 33.7 (CH2CH3), 31.6, 28.9, 27.9 (CH2 lactam), 24.8, 24.7 (CCH3) and 9.1 (CH2CH3); m/z (MH+ C12H23N2O2 requires 227.1760) 227.1767.

57. Single Step



61%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.28 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

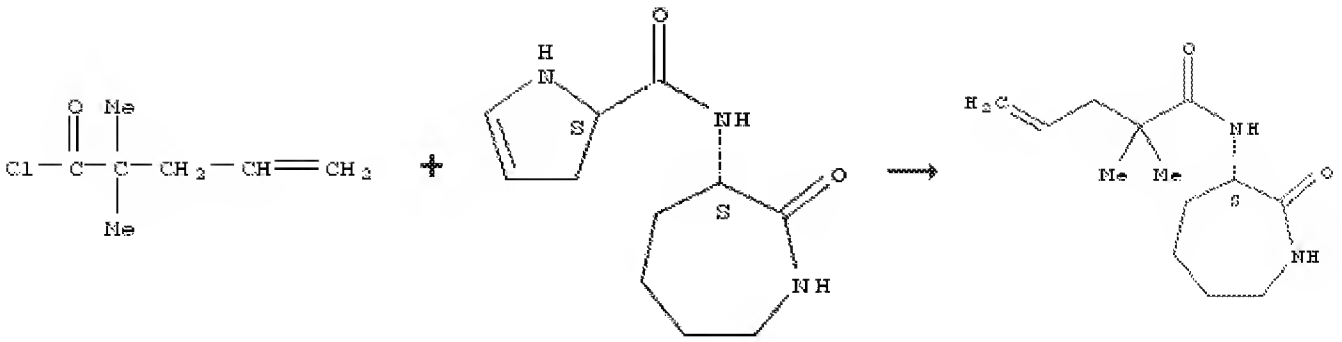
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 20: (S)-3-(2',2'-Dimethyl-propionyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (5 mmol) and Na2CO3 (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-propionyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2SO4 and reduced in vacuo. The residue was recrystallised from EtOAc/hexane to give (S)-3-(2',2'-dimethyl-propionyl)aminocaprolactam (645 mg, 61%). (S)-3-(2',2'-dimethyl-propionyl)aminocaprolactam, Yield (645 mg, 61%). m.p. 126-127 °C; [α]25D (c = 1, CHCl3) +39.5; νmax/cm-1 3381, 3255 (NH), 1680, 1632 (CO), 1506 (NH); δH (500 MHz, CDCl3) 7.10 (1H, d, J 5.0, CHNH), 6.75 (1H, br s, CH2NH), 4.42 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.27- 3.16 (2H, m, CH2NH), 2.03-1.89 (2H, m, 2 × ring CH), 1.83-1.71 (2H, m, 2 × ring CH), 1.45-1.28 (2H, m, 2 × ring CH) and 1.15 (9H, s, 3 × CH3); δ C (125 MHz, CDCl3) 177.7, 176.1 (CO), 52.1 (NHCHCO), 42.0 (CH2N), 40.5 (CCO), 31.5, 28.9, 27.9 (CH2 lactam), 27.4 (3 × CH3)· m/z (MNa+ C11H20N2O2Na requires 235.141699) 235.142237; (MH+ C11H21N2O2 requires 213.1597543) 213.160246.

58. Single Step



32%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

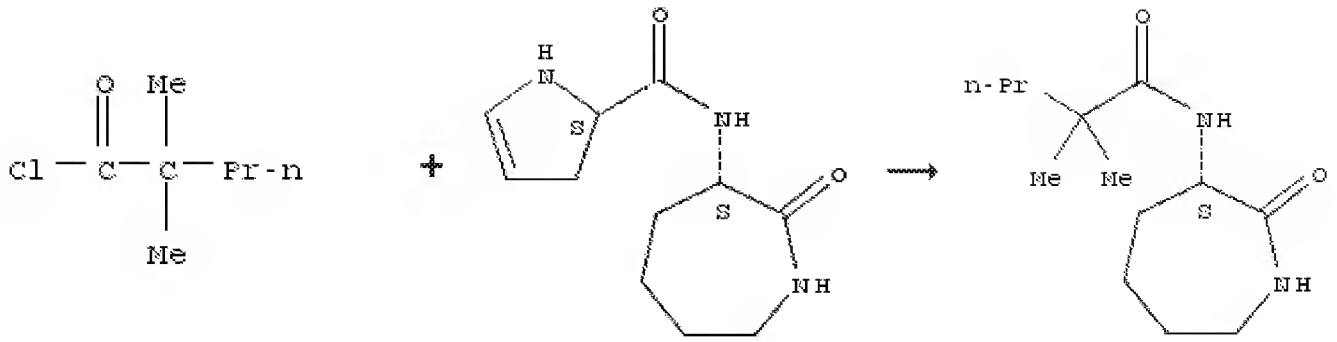
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 19 : (S)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na2CO3 (60 mmol) in water (50 ml) were added to a solution, of 2,2-dimethyl-pent-4-enoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3, and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexane to EtOAc) to give (S)-3-(2',2'-dimethyl-pent-4-enoyl)amino-caprolactam (1.43 g, 32%). (S)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam, Yield (1.43 g, 32%). m.p. 71-72 'C; [α]25D (c = 1, CHCl3)+27.7; vmax/cm-1 3395, 3304 (NH), 1675, 1633 (CO), 1534 (NH); δH (500 MHz, CDCl3) 7.10 (1H, d, J4.5, CHNH), 6.48 (1H, br s, CH2NR), 5.68 (1H, ddt, J 17, 10, 7.5, CH=CH2), 5.02 (1H, br d, J 17 CH=CHH), 5.00 (1H, br d, J10, CH=CHH), 4.45 (1H, dd, J11, 5.5, CHNH), 3.30-3.17 (2H, m, CH2NH), 2.27 (1H, J14, 7.5, CHHCH=CH2), 2.22 (1H, dd, J14, 7.5, CHHCH=CH2), 2.01 (1H, br d, J13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.85- 1.73 (2H, m, ring CH), 1.47-1.30 (2H, br m, ring CH ×2), 1.16 (3H, s, CMeMe) and 1.15 (3H, s, CMeMe); Se (125 MHz, CDCl3) 176.4, 175.9 (CO), 134.2 (CH CH2), 117.8 (CH=CH2), 52.1 (NHCHCO), 45.2, 42.1 (CH2), 41.9 (CMe2), 31.5, 28.9, 27.9 (CH,), 25.0 and 24.9 (CH3); m/z (M+ C13H22N2O2 requires 238.16813) 238.16834.

59. Single Step



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Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 12 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

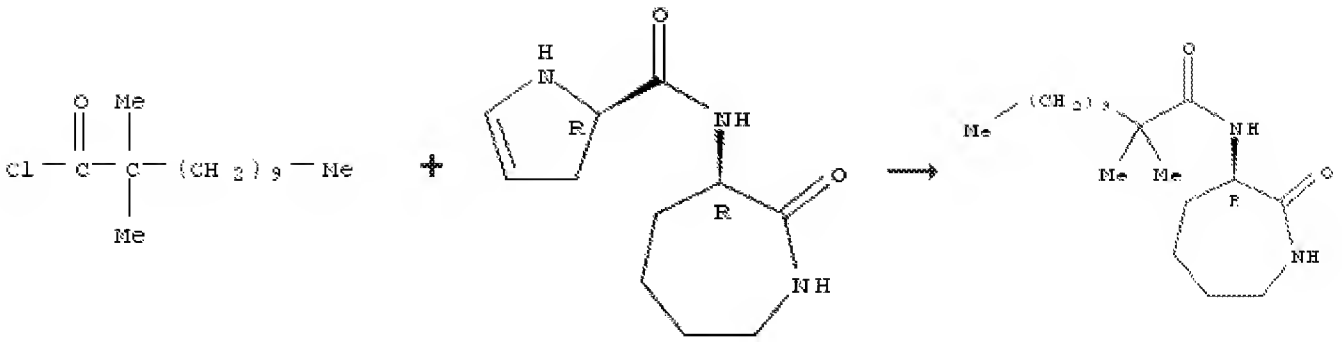
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 18 : (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na2CO3 (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pentanoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was recrystallised from EtOAc / hexane to give (S)-3-(2',2'-dimethylpentanoyl)amino-caprolactam (3.50 g, 77%) (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam, Yield (3.50 g, 77%). m.p. 84-85 °C; [α]25D (c = 1, CHCl3) +30.7; vmax/cm-1 3387, 3239 (NH), 1655, 1634 (CO), 1507 (NH); δH (500 MHz, CDCl3) 7.08 (1H, d, J5, CHNH), 6.53 (1H, br s, CH2NH), 4.45 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.00 (1H, br d, J13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.84-1.73 (2H, m, ring CH), 1.47-1.30 (4H, br m, ring CH ×2 + CH2CMe2CONH), 1.23-1.15 (2H, m, CH2CH3) 1-14 (3H, s, CMeMe), 1.13 (3H, s, CMeMe) and 0.84 (3H, t, J7, CH2CH3); δc (125 MHz, CDCl3) 177.0, 176.1 (CO), 52.1 (NHCHCO), 43.6, 42.0 (×2, one of which is CMe2), 31.5, 28.9, 27.9 (CH2), 25.3, 25.2 (CH3), 18.0 (CH2) and 14.5 (CH3); m/z (M+ C13H24N2O2 requires 240.18378) 240.18437.

60. Single Step



76%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

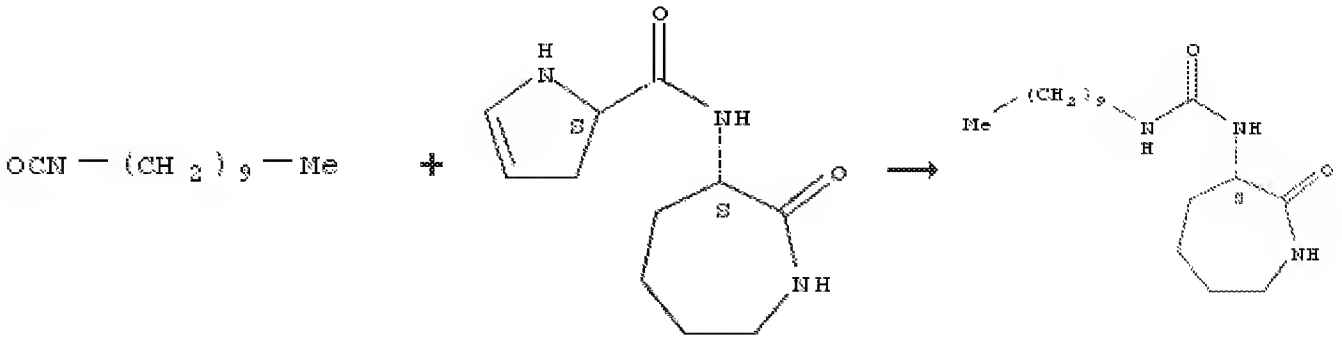
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 17: (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam: (R,R)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (EtOAc: hexanes 1:3 to EtOAc) to give (R)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam (515 mg, 76%). Compound 17 was later resynthesised on a larger scale, and this batch of material had the following properties: (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam, Yield (515 mg, 76%). m.p. 48-49 °C; [α]25D (c = 1, CHCl3) -25.7; [α]25D (c = 0.5, MeOH) -12.2

61. Single Step



64%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.26 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

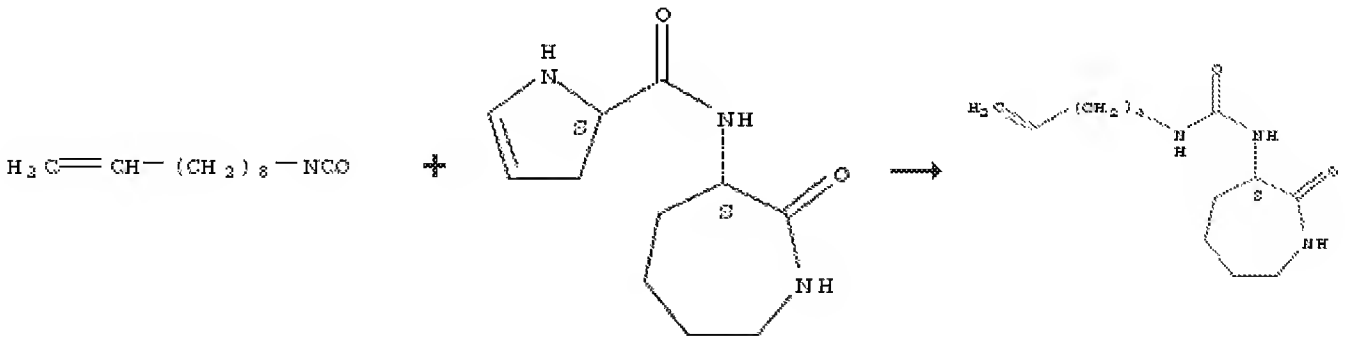
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 16: (S)-3-(decylaminocarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of decyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (401 mg, 64%). (S)-3-(decylaminocarbonyl)amino-caprolactam, Yield (401 mg, 64%). Melting point: 97-98 °C. [α]25D (c=1,CHCl3) = +27.7. IR: νmax (cm4): 3359, 3316 (NH), 1621, (CO), 1558 (NH). 1H NMR (δH 500 MHz, CDCl3): 6.62 (1H, br s, ring CH2NH), 6.09 (1H, d, J 6 CHNH), 5.16 (1H, br t, J5, urea CH2NH), 4.48 (1H, ddd, J 11, 6, 1, NHCHCO), 3.26 (1H, ddd, J16, 11, 5, ring CH2N), 3.17 (1H, dt, J15, 7, ring CH2N), 3.11-3.02 (2H, m, urea NHCH2), 2.02 (1H, br d J14, ring CH), 1.96-1.87 (1H, m, ring CH), 1.83-1.70 (2H, m, ring CH), 1.48-1.27 (4H, br m, ring CH x2 + chain CH2), 1.27- 1.14 (14H, m, (CH2)) and 0.82 (3H, t, J 7, CH3). 13C NMR (δc, 125 MHz, CDCl3): 177.2, 157.6 (CO), 52.7 (NHCHCO), 42.1, 40.4 (NCH2), 32.9, 31.8, 30.2, 29.6, 29.5, 29.4, 29.3, 28.8, 27.9, 26.9, 22.6 (CH2) and 14.1. m/z (C17H33N3O2Na): 334.24880 (calculated: 334.2470).

62. Single Step



56%

Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.25 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

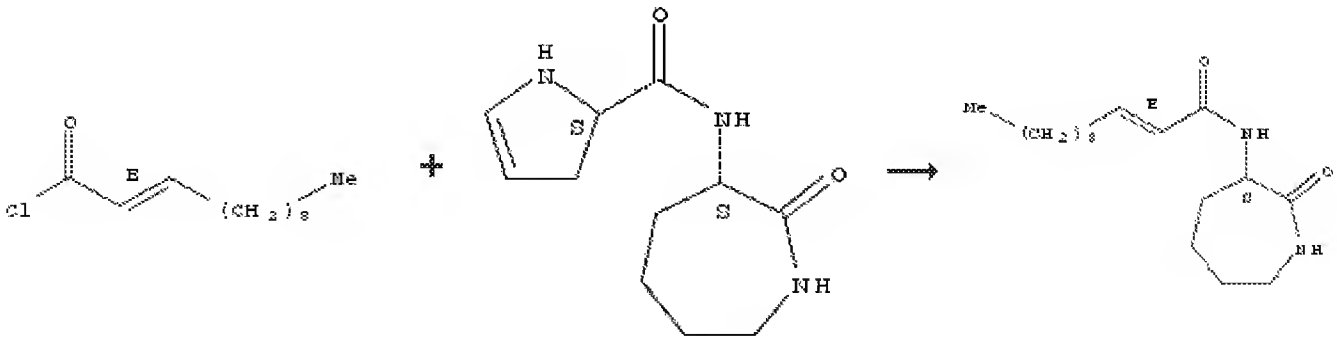
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 15: (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of dec-9-enyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (347 mg; 56%). (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam: yield (347 mg; 56%). Melting point: 98-99 °C. [α]25D (c=1,CHCl3) = +27.3. IR: νmax (cm-1): 3365, 3327, 3276 (NH), 1619, (CO), 1551 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.64 (1H, br s, ring CH2NH), 6.12 (1H, d, J6 CHNH), 5.75 (1H, ddtd, J17, 10, 6.5, 1.5, CH2=CH), 5.21-5.12 (1H, br m, urea CH2NH), 4.93(1H, dq,J17,1.5,CHH=CH),4.87(1H,brd,J10,CHH=CH),4.49(1H, dd,J 11, 6, NHCHCO), 3.25 (1H, ddd, J 15.5, 12, 4, ring CH2N), 3.17 (1H, dt, J14, 6, ring CH2N), 3.11-3.02 (2H, m, urea NHCH2), 2.05-1.87 (4H, br m, ring CH ×2 + CH2CH=CH), 1.82-1.70 (2H, m, ring CH), 1.48-1.36 (3H, br m, chain CH2CH2NH, + ring CH), 1.36-1.27 (3H, m, ring CH + chain CH2) and 1.27-1.17 (8H, m, chain (CH2)4). 13C NMR (δc, 125 MHz, CDCl3): 177.2, 157.6 (CO), 139.1, 114.1 (CH=CH), 52.7 (NHCHCO), 42.1, 40.3 (NCH2), 33.7, 32.9, 30.3, 29.4, 29.3, 29.0, 28.8 (x2), 27.9 and 26.9 (CH2)· m/z (C17H31N3O2Na): 332.23150 (calculated: 332.2314).

63. Single Step



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Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.24 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

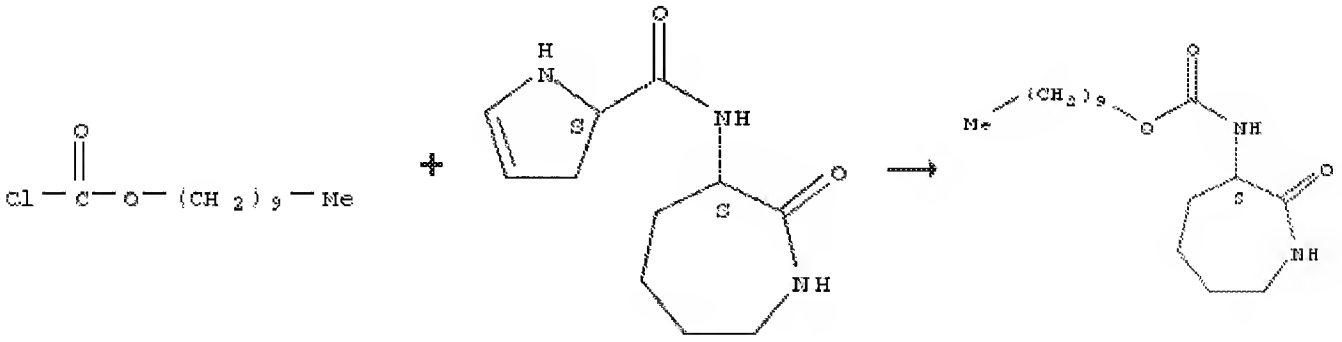
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 14: (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of dodec-2-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (472 mg; 77%). (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam: Yield (472 mg; 77%). Melting point: 87-88 °C. [α]25D (c=1,CHCl3) = +44.7. IR: vmax (cm-1): 3382, 3331 (NH), 1660, 1616 (CO), 1520 (NH). 1H NMR (δH 500 MHz, CDCl3): 6.94 (1H, d, J 5.5, CHNH), 6.84 (1H, br s, CH2NR), 6.78 (1H, dt, J15.5, 7, CH2CH=CH), 5.80 (1H, d, J 15.5, CH2CH=CH), 4.56 (1H, ddd, J11, 6, 1.5, CHNH), 3.29-3.15 (2H, m, CH2NH), 2.11 (2H, q, J7, CH2CH-CH), 2.07 (1H, br d, J13.5, ring CH), 1.98-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.44 (1H, br qd, J14, 2.5, ring CH), 1.41-1.29 (3H, br m, ring CH + CH2CH2CH-CH), 1.29-1.14 (12H, m, (CH2)6) and 0.82 (3H, t, J 6.5, CH3)· 13C NMR (δc, 125 MHz, CDCl3): 175.9, 165.0 (CO), 144.8, 123.5 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH2), 32.0, 31.8, 31.6, 29.4 (x2), 29.2, 29.1, 28.8, 28.2, 27.9, 22.6 (CH2) and 14.1 (CH3)- m/z (C18H32N2O2Na): 331.23570 (calculated: 331.2361).

64. Single Step



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Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.24 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

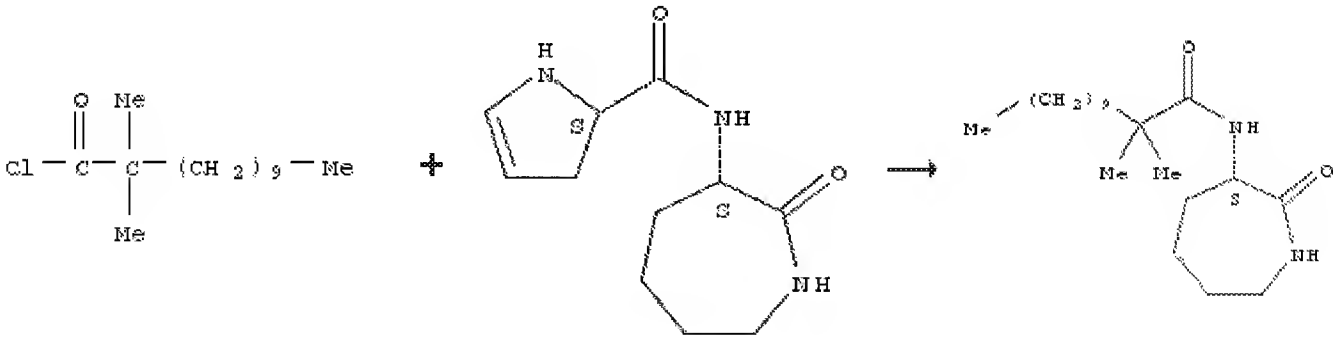
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 13: (S)-3-(decyloxycarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of decyl chloroformate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (459 mg; 74%). (S)-3-(decyloxycarbonyl)amino-caprolactam, Yield (459 mg; 74%). Melting point: 40-41 °C. [α]25D (c=1,CHCl3) = +31.4. IR: νmax (cm-1): 3352,3300 (NH), 1682,1657, 1637 (CO), 1513 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.86 (1H, br s, CH2NH), 6.72 (1H, d, J 6 CHNH), 4.49 (1H, dd, J 11, 6, CHNH), 3.99 (2H, t, J 6, OCH2), 3.26-3.14 (2H, m, CH2NH), 2.04 (1H, br d, J13.5, ring CH), 2.00-1.91 (1H, m, ring CH), 1.82-1.68 (2H, m, ring CH), 1.55 (2H, br gn J 7.0, CH2CH2O), 1.48 (1H, br qd, J 14, 2.5, ring CH), 1.38-1.31 (1H, br m, ring CH), 1.29-1.17 (14H, m, (CH2)4) and 0.83 (3H, t, J7, CH3)- 13C NMR (δc, 125 MHz, CDCl3): 175.8, 155.9 (CO), 65.0 (OCH2), 53.5 (NHCHCO), 42.0 (NCH2), 32.1, 31.8, 29.5 (x2), 29.2 (×2), 29.0, 28.8, 28.0, 25.8, 22.6 (CH2) and 14.1 (CH3)· m/z (C27H32N2O3Na): 335.23190 (calculated: 335.2311).

65. Single Step



80%

Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.23 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

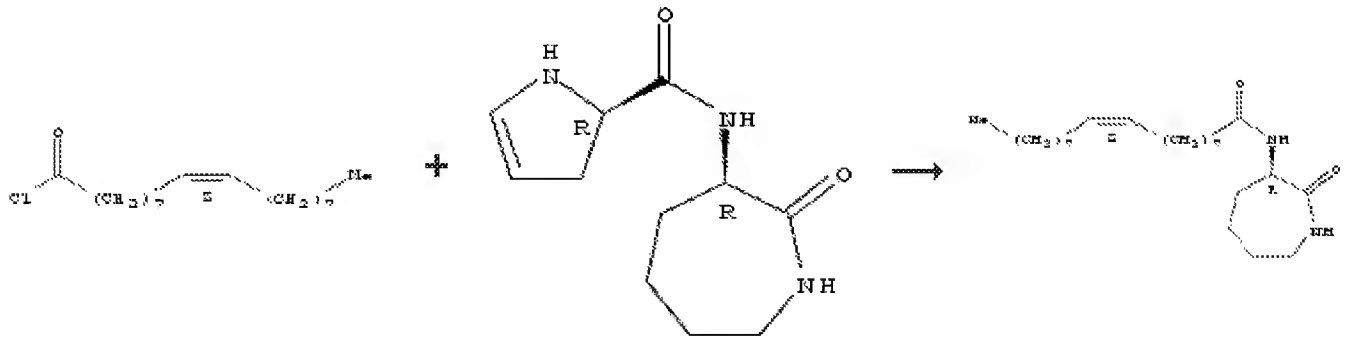
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 12: (5)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (543 mg; 80%). (5)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam: Yield (543 mg; 80%). Compound 12 was later resynthesised on a larger scale, and this batch of material had the following properties Melting point: 41-42 °C. [α]25D (c=1,CHCl3) = +28.0. IR: νmax (cm4): 3403, 3265 (NH), 1673, 1641 (CO), 1497 (NH). 1H NMR (δH 500 MHz, CDCl3): 7.08 (1H, d, J5.5, CHNH), 6.67 (1H, br s, CH2NH), 4.44 (1H, dd, J11, 5.5, CHNH), 3.28-3.15 (2H, m, CH2NH), 2.01 (1H, br d, J13, ring CH), 1.98-1.89 (1H, m, ring CH), 1.84-1.72 (2H, m, ring CH), 1.47- 1.30 (3H, br m, ring CH + CH2CMe2CONH), 1.27-1.15 (17H, br m, ring CH +(CH2)8) 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.82 (3H, t, J7, CH2CH3)· 13C NMR (δc, 125 MHz, CDCl3): 177.1, 176.0 (CO), 52.0 (NHCHCO), 41.9 (CMe2), 42.1, 41.3, 31.8, 31.5, 30.1, 29.6, 29.5 (x2), 29.3, 28.9, 27.9 (CH2), 25.3, 25.2 (CH3), 24.8, 22.6 (CH2) and 14.1 (CH3)· m/z (C20H38N2O2Na): 361.28350 (calculated: 361.2831). melting point 51-52 °C. [α]25D (c = 1, CHCl3) +28.0; [α]25D (c = 0.87, MeOH) +13.3.

66. Single Step



73%

Overview

Steps/Stages **Notes**

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

1) reaction from p.23 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

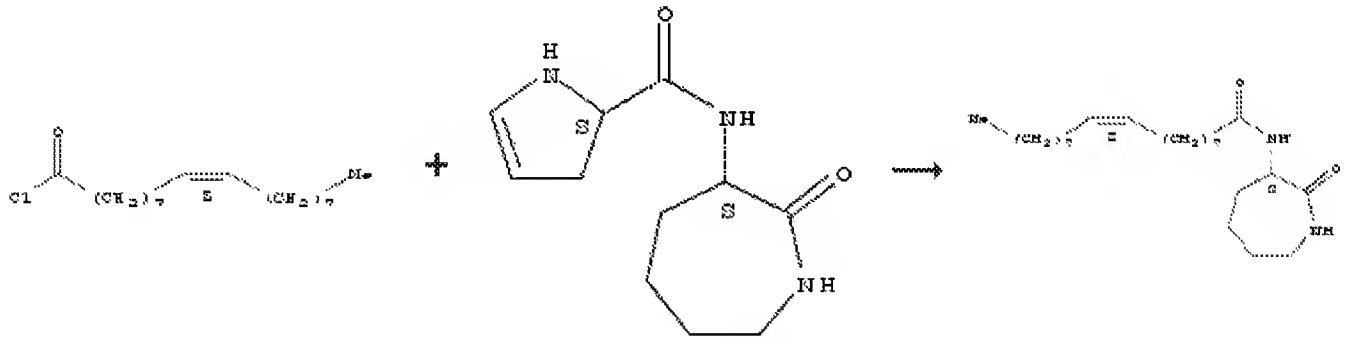
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 11: (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam:(R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of (Z)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (574 mg; 73%). (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam: Yield (574 mg; 73%). Melting point: 66-67 °C. [α]25D (c=1,CHCl3) = -31.4.

67. Single Step



66%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.22 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

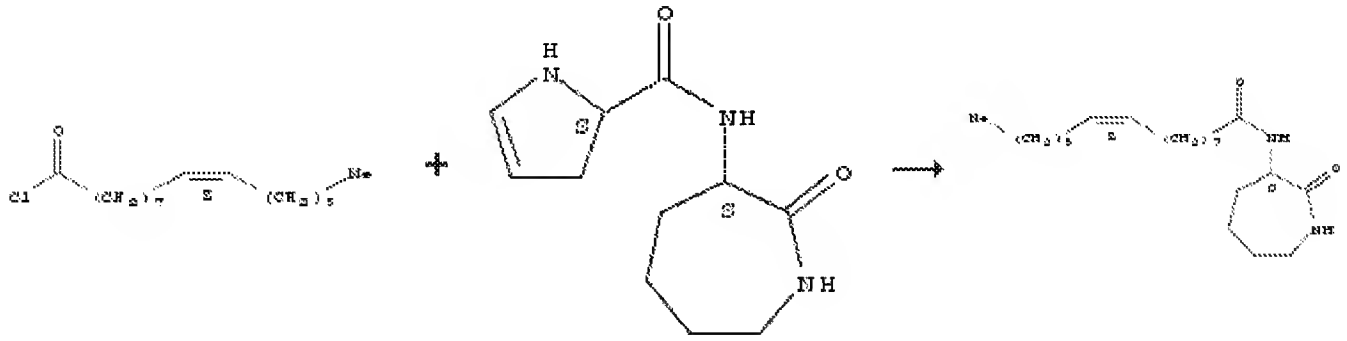
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 10: (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of (Z)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (514 mg; 66%). (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam, Yield (514 mg; 66%). Melting point: 66-67 °C. [α]25D (c = 1, CHCl3) = +30.9. IR: vmax (cm-1): 3327, 3268 (NH), 1655, 1631 (CO), 1523 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.88 (1H, d, J 5.5, CHNH), 6.74 (1H, br t, J 5, CH2NH), 5.33-5.24 (2H, m, CH=CH), 4.49 (1H, ddd, J 11, 6, 1.5, CHNH), 3.29-3.14 (2H, m, CH2NH), 2.16 (2H, t, J7.5, CH2CONH), 2.03 (1H, br d, J13.5, ring CH), 1.99-1.89 (5H, m, ring CH + CH2CH=CHCH2), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br gn J7.0, CH2CH2CONH), 1.42 (1H, br qd, J14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (20H, m, (CH2)6CH2CH=CHCH2(CH2)4) and 0.83 (3H, t, J 7, CH3)· 13C NMR (δc, 125 MHz, CDCl3): 175.9, 172.3 (CO), 129.9. 129.7 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH2), 36.6, 31.8, 31.7, 29.7 (x2), 29.5, 29.3 (x3), 29.2, 29.1, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH2) and 14.1 (CH3)· m/z (C24H44N2O2Na): 415.32820 (calculated: 415.3300).

68. Single Step



56%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.21 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

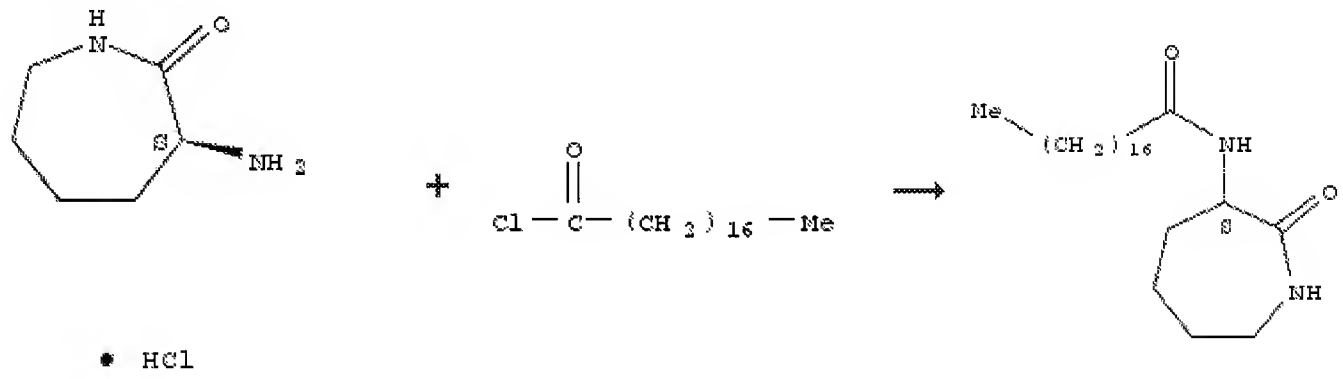
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 9: (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na2CO3 (6 mmol) in. water (25 ml) were added to a solution of (Z)-hexadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (406 mg; 56%). (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam, yield (406 mg; 56%) (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam. Melting point: 67-68 °C. [α]25D (c = 1 , CHCl3) = +33.2. IR: vmax (cm-1): 3324, 3268 (NH), 1655, 1630 (CO), 1524 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.88 (1H, d, J 5.5, CHNH), 6.67 (1H, br s, CH2NH), 5.33-5.25 (2H, m, CH=CH), 4.50 (1H, ddd, J11, 6, 1, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.17 (2H, t, J7.5, CH2CONH), 2.03 (1H, br d, J13, ring CH), 1.99-1.90 (5H, m, ring CH + CH2CH=CHCH2), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br qn J 7.0, CH2CH2CONH), 1.43 (1H, br qd, J 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (16H, m, (CH2)4CH2CH=CHCH2(CH2)4) and 0.84 (3H, t, J7, CH3)-13C NMR (δc, 125 MHz, CDCl3): 175.9, 172.3 (CO), 129.8 (x2) (CH=CH), 52.0 (NHCHCO), 42.0 (NCH2), 36.6, 31.7 (x2), 29.7 (x2), 29.2 (x2), 29.1, 29.0, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH2) and 14.1 (CH3)- m/z (C22H40N2O2Na): 387.29700 (calculated: 387.2987).

69. Single Step



82%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) regioselective, reaction from p.20 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

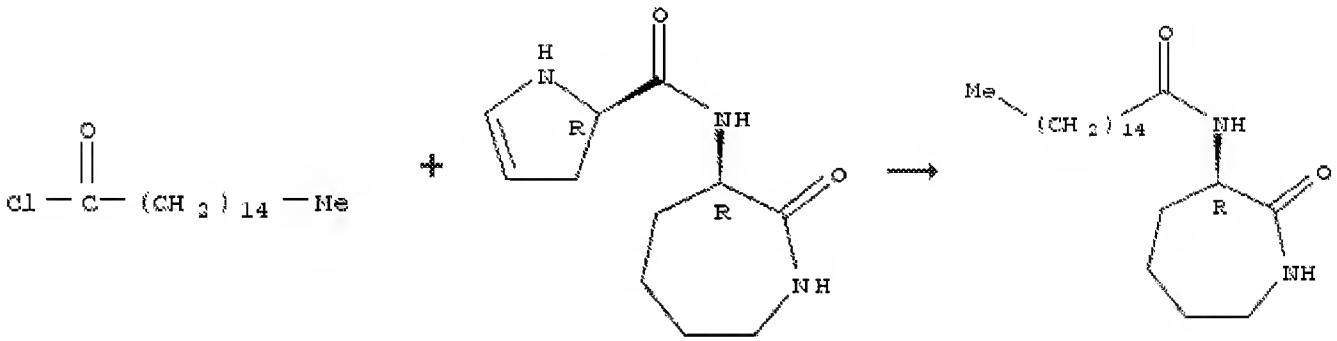
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 8: (S)-3-octadecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of octadecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (648 mg; 82%). (S)-3-octadecanoylamino-caprolactam: Yield (648 mg; 82%). Melting point: 87-88 °C. [α]25D (c = 1 , CHCl3) = +31.9. IR: vmax (cm-1): 3327, 3272 (NH), 1667,1655, 1631 (CO), 1524 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.88 (1H, d, J 5.5, CHNH), 6.72-6.58 (1H, br m, CH2NH), 4.50 (1H, dd, J 11, 6, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.17 (2H, t, J 7.5, CH2CONH), 2.03 (1H, br d, J 13, ring CH), 1.99-1.90 (1H, m, ring CH), 1.86- 1.73 (2H, m, ring CH), 1.58 (2H, br qn J7.0, CH2CH2CONH), 1.42 (1H, br qd, J 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (28H, m, (CH2);4) and 0.84 (3H, t, J 6.5, CH3). 13C NMR (δc, 125 MHz, CDCl3): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH2), 36.6, 31.9, 31.7, 29.6 (×8), 29.4, 29.3 (×2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH2) and 14.1 (CH3)- m/z (C24H46N2O2Na): 417.34460 (calculated: 417.3457).

70. Single Step



67%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.20 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

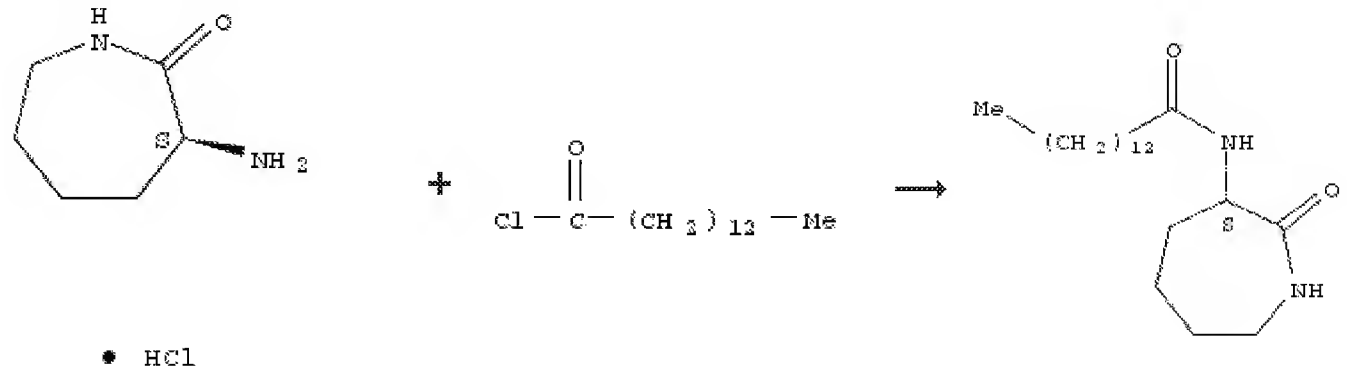
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 7: (R)-3-hexadecanoylamino-caprolactam: (R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na2CO3 (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (1.23 g; 67%). (R)-3-hexadecanoylamino-caprolactam, Yield (1.23 g; 67%). Melting point: 99-100 °C. [α]25D (c=1,CHCl3) = -32.0.

71. Single Step



61%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) regioselective, reaction from p.19 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

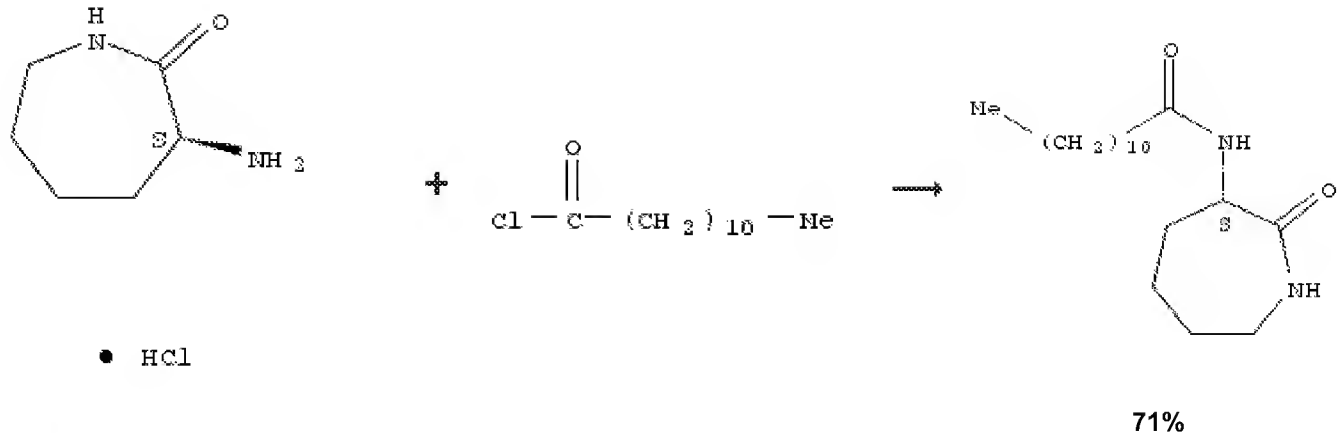
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 6: (S)-3-tetradecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of tetradecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (412 mg; 61%). (S)-3-tetradecanoylamino-caprolactam, Yield (412 mg; 61%). Melting point: 97-98 °C. [α]25D (c=1,CHCl3) = +33.2. IR: vmax (cm-1): 3326, 3273 (NH), 1666, 1655, 1631 (CO), 1523 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.87 (1H, d, J 5.5, CHNH), 6.66-6.48 (1H, br m, CH2NH), 4.50 (18, dd, J 11, 6, CHNH), 3.30-3.16 (2H, m, CH2NH), 2.18 (2H, t, J 7.5, CH2CONH), 2.04 (1H, br d, J 13.5, ring CH), 2.00-1.92 (1H, m, ring CH), 1.86-1.74 (2H, m, ring CH), 1.59 (2H, br qn J 7.0, CH2CH2CONH), 1.43 (1H, br q, J12.5, ring CH), 1.31 (1H, br q, J13, ring CH), 1.31-1.13 (20H, m, (CH2)10) and 0.85(3H, t,J6.5, CH3). 13C NMR (δc, 125 MHz, CDCl3): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH2), 36.6, 31.9, 31.7, 29.6 (×4), 29.4, 29.3 (x2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH2) and 14.1 (CH3), m/z (C20H35N2O2Na): 361.28270 (calculated: 361.2831).

72. Single Step



• HCl

71%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.19 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

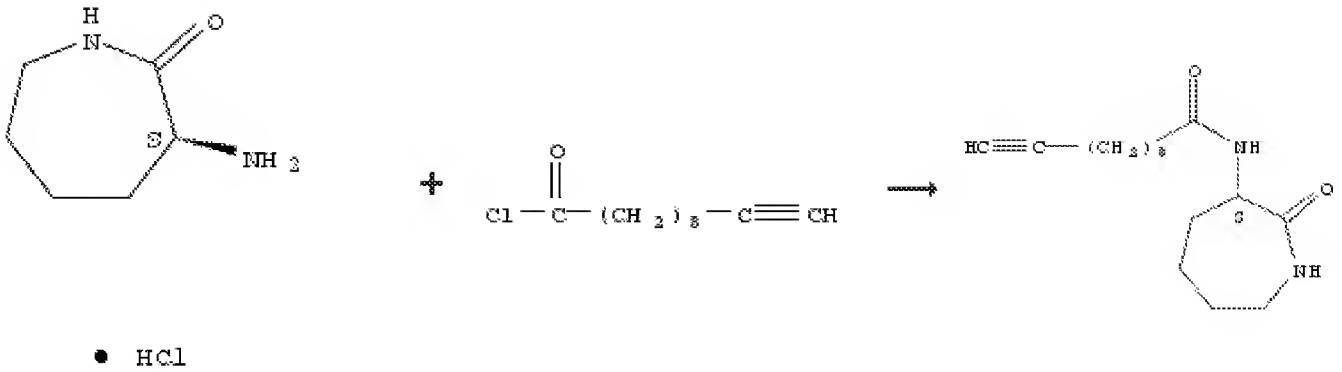
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 5: (S)-3-dodecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give the title compound (439 mg, 71%). (S)-3-dodecanoylamino-caprolactam, Yield (439 mg, 71%). Melting point: 93-94 °C. [α]25D (c=1,CHCl3) = +35.5. IR: νmax (cm-1): 3324, 3267 (NH), 1666, 1630 (CO), 1521 (NH). 1H NMR (δH, 500 MHz, d6-DMSO): 7.76 (1H, br s, CH2NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J10.5, 7.5, CHNH), 3.15 (1H, ddd, J15.5, 11.5, 5, CHHNH), 3.05 (1H, dt, J 14.5, 5.5, CHHNH), 2.17-2.07 (2H, m, CH2CONH), 1.90- 1.80 (1H, m, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, J 12, 3.5, C-5 H), 1.46 (2H, br qn J 6.0, CH2CH2CONH), 1.36 (1H, qd, J 12.5, 2.5, C-4 H), 1.31-1.13 (17H, m, (CH2)8 + C-6 H) and 0.85 (3H, t, J 6.5, CH3)· 13C NMR (δc, 125 MHz, d6-DMSO): 174.4 (CO-ring), 171.2 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH2), 35.3, 31.4, 31.3, 29.1 (×3), 29.0 (x2), 28.8, 28.7, 27.8, 25.4, 22.2 (CH2) and 14.0 (CH3)· m/z (C18H34N2O2Na): 333.25150 (calculated: 333.2518).

73. Single Step



• HCl

62%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.18 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

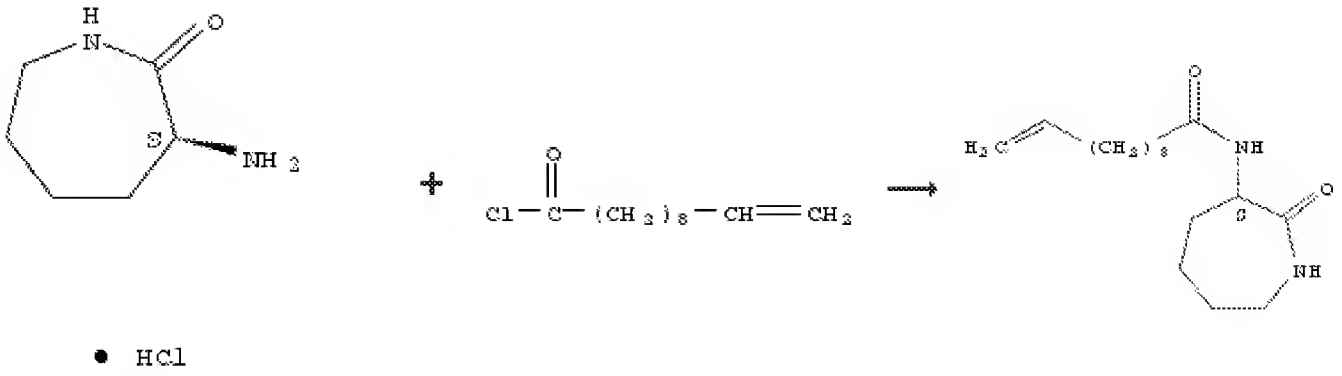
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 4: (S)-3-(undec-10-ynoyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of undec-10-ynoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give the title compound (362 mg; 62%). (S)-3-(undec-10-ynoyl)amino-caprolactam, Yield (362 mg; 62%). Melting point: 73-75 °C. [α]25D (c=1,CHCl3) = +42.1. IR: vmax (cm-1): 3332, 3295 (NH), 1667, 1633 (CO), 1523 (NH). 1H NMR (δH, 500 MHz, d6-DMSO): 7.76 (1H, t, 75.5, CH2NH), 7.68 (1H, d, 77, CHNH), 4.36 (1H, dd,J11, 7, CHNH), 3.16 (1H, ddd, J15.5,11.5, 5, CHHNH), 3.03 (1H, br dt, J14, 7, CHHNH), 2.17-2.07 (4H, m, CH2CONH + CH2CCH), 1.85 (1H, m, C-5 H), 1.77-1.67 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, J 13, 3.0, C- 5 H), 1.50-1.28 (5H, m, CH2CH2CONH + HCCCH2CH2+ C-4 H) and 1.28-1.13 (9H, m, (CH2)4 + C-6 H). 13C NMR (δc, 125 MHz, d6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 84.6 (CH2CCH), 71.1 (CH2CCH), 51.3 (NHCHCO), 40.7 (NCH2), 35.2, 31.3, 29.0, 28.8, 28.7, 28.5, 28.2, 28.0, 27.8, 25.4 and 17.8 (CH2). m/z (C17H28N2O2Na): 317.20470 (calculated: 315.2048).

74. Single Step



• HCl

72%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.17 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

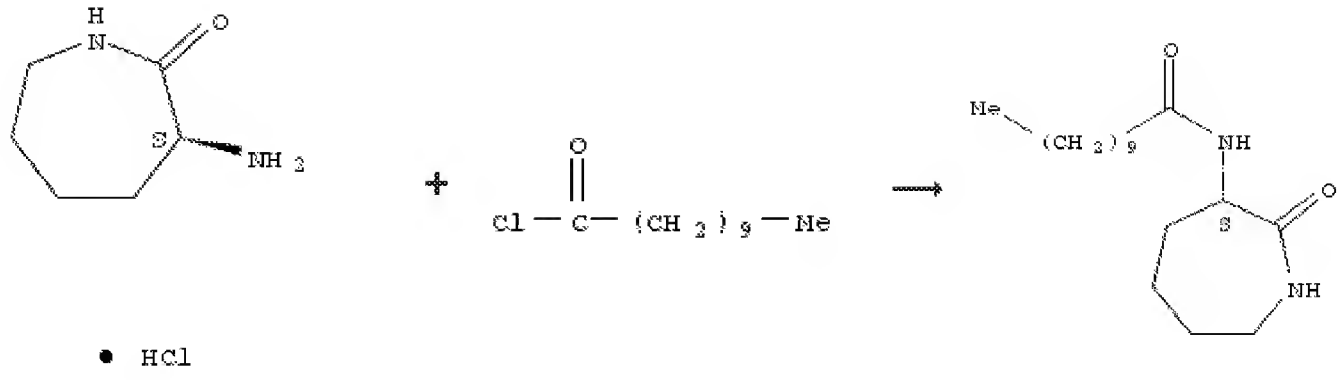
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 3: (S)-3-(undec-10-enoyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of undec-10-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 horns. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give the title compound (423 mg; 72%). (S)-3-(undec-10-enoyl)amino-caprolactam, Yield (423 mg; 72%). Melting point: 83-84 °C. [α]25D (c=1, CHCl3) = +40.1. IR: vmax (cm-1): 3327, 3273 (NH), 1655, 1630 (CO), 1521 (NH). 1H NMR (δH, 500 MHz, d6-DMSO): 7.75 (1H, t, J6, CH2Nfl), 7.66 (1H, d, J7, CHNH), 5.76 (1H, ddt, J17, 10, 6.5 CH2=CH), 4.96 (1H, dq, J17, 2, CHH=CH), 4.96 (1H, ddt, J17, 2, 1, CHH=CH), 4.36 (1H, dd, J10, 7, CHNH), 3.14 (1H, ddd, J15.5, 11.5, 5, CHHNH), 3.03 (1H, br dt, J13, 5.5, CHHNH), 2.16-2.06 (2H, m, CH2CONH), 1.98 (2H, br q, J7, CH2=CHCH2), 1.85 (1H, dt, J10.5, 3, C-5 H), 1.75-1.67 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, J 13, 3.5, C-5 H), 1.44 (2H, br qn, J 7, CH2CH2CONH), 1.39-1.27 (3H, m, CH2=CHCH2CH2 + C-4 H) and 1.31-1.13 (9H, m, (CH2)4+ C-6 H). 13C NMR (δc, 125 MHz, d6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 138.9 (CH2=CH), 114.7 (CH2=CH), 51.3 (NHCHCO), 40.7 (NCH2), 35.3, 33.3, 31.3, 29.0, 28.9 (x2) 28.7, 28.6, 28.4, 27.8 and 25.4 (CH2)- m/z (C17H30N2O2Na): 317.21970 (calculated: 317.2205).

75. Single Step



• HCl

67%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.17 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

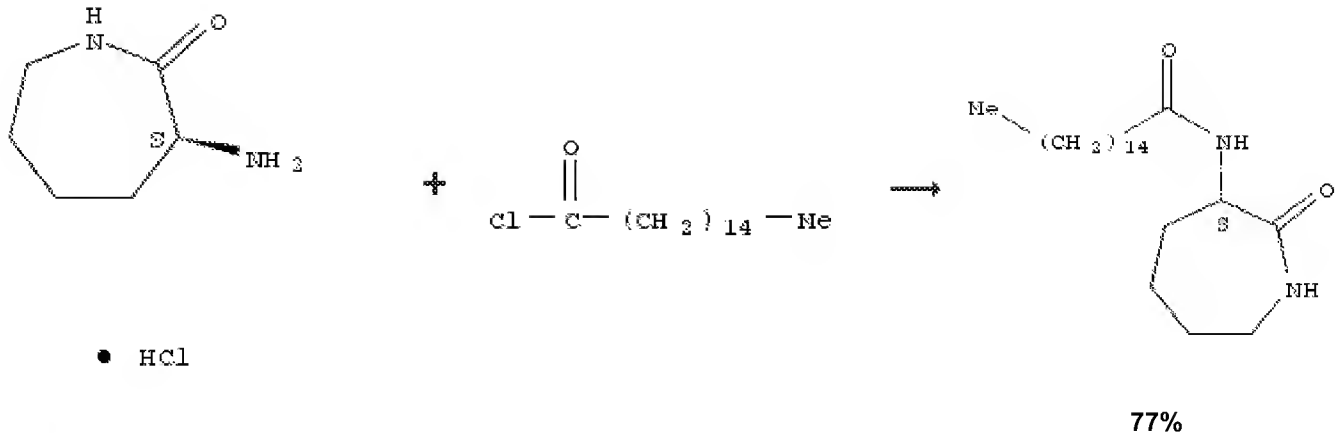
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 2: (S)-3-undecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na2CO3 (6 mmol) in water (25 ml) were added to a solution of undecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (397 mg, 67%). (S)-3-undecanoylamino-caprolactam, Yield (397 mg, 67%). Melting point: 91-92 °C. [α]25D (c = 1, CHCl3) = +30.2. 1R: vmax (cm-1): 3342, 3313 (NH), 1676, 1638 (CO), 1519 (NH); 3342, 3292 (NH), 1671, 1639 (CO), 1513 (NH). 1H NMR (δH, 500 MHz, d6-DMSO): 7.76 (1H, t, J 6, CH2NR), 7.68 (1H, d, J7, CHNH), 4.38 (1H, dd, J10, 7, CHNH), 3.15 (1H, ddd, J15.5, 11, 5, CHHNH), 3.04 (1H, dt, J13, 6, CHHNH), 2.19-2.06 (2H, m, CH2CONH), 1.85 (1H, dt, J10.5, 3, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br gn J6.5, CH2CH2CONH), 1.35 (1H, qd, J12.5, 3, C-4 H), 1.31-1.13 (15H, m, (CH2)7 + C-6 H) and 0.85 (3H, t, J7.0, CH3), 13C NMR (8c, 125 MHz, d6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH2), 35.2, 31.4, 31.3, 29.1, 29.0 (×2), 28.9, 28.8, 28.7, 27.8, 25.4, 22.2 (CH2) and 14.0 (CH3)- m/z (C17H32N2O2Na): 319.23540 (calculated: 319.2361).

76. Single Step



• HCl

77%

Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H_2O, S:CH_2Cl_2, 2 h, rt

Notes

1) reaction from p.16 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 1: (S)-3-hexadecanoylamino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na2CO3 (15 nrniol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na2CO3 and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (1.41 g; 77%). (S)-3-hexadecanoylamino-caprolactam, Yield (1.41 g; 77%). Melting point: 99-100 °C. [α]25 D(c=1,CHCl3) = +32.0. IR: νmax (cm-1) : 3325, 3272 (NH), 1666, 1655, 1631 (CO), 1524 (NH). 1H NMR (δH, 500 MHz, CDCl3): 6.88 (1H, d, J5.5, CHNH), 6.72 (1H, br s, CH2NH), 4.49 (1H, ddd, J11, 6,1, CHNH), 3.29-3.16 (2H, m, CH2NH), 2.17 (2H, t, J 7 . 5 , CH2CONH), 2.03 (1H, br d, .713.5, ring CH), 1.98-1.89 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.58 (2H, br qn J7.0, CH2CH2CONH), 1.43 (1H, br qd, J14, 3, ring CH), 1.38-1.29 (1H, br m, ring CH), 1.29-1.14 (24H, m, (CH2)12) and 0.83 (3H,t, .76.5, CH3). 13C NMR (8c 125 MHz, CDCl3): 175.9,172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH2), 36.6, 31.9, 31.7, 29.6 (x6), 29.4, 29.3 (x2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH2) and 14.1 (CH3). m/z (C22H42N2O2Na): 389.31450 (calculated: 389.3144).